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ORIGINAL RESEARCH

Ultrasound-guided versus fluoroscopy-guided large-bore femoral access in PCI of complex coronary lesions: the international, multicentre, randomised ULTRACOLOR Trial

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ABSTRACT

BACKGROUND: Transfemoral access is often used when large-bore guide catheters are required for percutaneous coronary intervention (PCI) of complex coronary lesions, especially when large-bore transradial access is contraindicated. Whether the risk of access site complications for these procedures may be reduced by ultrasound-guided puncture is unclear.

AIMS: We aimed to show the superiority of ultrasound-guided femoral puncture compared to fluoroscopy-guided access in large-bore complex PCI with regard to access site-related Bleeding Academic Research Consortium 2, 3 or 5 bleeding and/or vascular complications requiring intervention during hospitalisation.

METHODS: The ULTRACOLOR Trial is an international, multicentre, randomised controlled trial investigating whether ultrasound-guided large-bore femoral access reduces clinically relevant access site complications compared to fluoroscopy-guided large-bore femoral access in PCI of complex coronary lesions.

RESULTS: A total of 544 patients undergoing complex PCI mandating large-bore (≥7 Fr) transfemoral access were randomised at 10 European centres (median age 71; 76% male). Of these patients, 68% required PCI of a chronic total occlusion. The primary endpoint was met in 18.9% of PCI with fluoroscopy-guided access and 15.7% of PCI with ultrasound-guided access (p=0.32). First-pass puncture success was 92% for ultrasound-guided access versus 85% for fluoroscopy-guided access (p=0.02). The median time in the catheterisation laboratory was 102 minutes versus 105 minutes (p=0.43), and the major adverse cardiovascular event rate at 1 month was 4.1% for fluoroscopy-guided access and 2.6% for ultrasound-guided access (p=0.32).

CONCLUSIONS: As compared to fluoroscopy-guided access, the routine use of ultrasound-guided access for large-bore transfemoral complex PCI did not significantly reduce clinically relevant bleeding or vascular access site complications. A significantly higher first-pass puncture success rate was demonstrated for ultrasound-guided access. ClinicalTrials.gov identifier: NCT04837404

KEYWORDS: complex PCI; CTO; large bore; ultrasound; vascular access

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During complex percutaneous coronary intervention (PCI), large-bore (7 or 8 Fr) guide catheters are often preferred. They provide improved backup support and better compatibility with the equipment necessary to treat complex lesions, including heavily calcified lesions, left main lesions, complex bifurcations and chronic total occlusions (CTOs)[1,2]. As compared to transfemoral access (TFA), recent studies have demonstrated the feasibility and increased safety of large-bore transradial access (TRA) for complex PCI[3,4]. However, contraindications for large-bore TRA are not uncommon, including the presence of a small radial artery, known severe spasm, or anatomical variants. In these cases, large-bore TFA is needed. Previous studies have shown a high risk of clinically relevant bleeding or vascular complications when large-bore TFA is applied for complex PCI[5,6]. Routine use of ultrasound-guided puncture has been shown to lower the risk of a suboptimal puncture height as well as the risk of puncture in a calcified plaque, which are both associated with higher complication rates and failure of vascular closure devices (VCDs)[7-10]. However, ultrasound-guided puncture of the femoral artery in coronary procedures, even in large-bore access for complex PCI, is not routinely applied, likely owing to the lack of robust evidence. In the recent Routine Ultrasound Guidance for Vascular Access for Cardiac Procedures (UNIVERSAL) randomised clinical trial, the use of ultrasound-guided femoral access did not significantly reduce bleeding or vascular complications, when compared to standard (fluoroscopy-guided) access[11]. Of note, the proportion of complex PCI in this trial was low, and 6 Fr access was mainly used. Whether ultrasound guidance has a potentially greater benefit on access site complications in a patient population undergoing transfemoral PCI with large-bore guide catheters (≥7 Fr) remains unknown.

Editorial, see page e837

Impact on daily practice

Transfemoral access (TFA) remains commonly used when large-bore guide catheters are required for percutaneous coronary intervention (PCI) of complex coronary lesions, especially when large-bore transradial access is contraindicated. Whether the risk of access site complications for these procedures may be reduced by ultrasound-guided puncture is unclear. As compared to fluoroscopy guidance, the routine use of ultrasound guidance for large-bore TFA in complex PCI did not reduce clinically relevant bleeding or vascular complications. Ultrasound guidance was associated with an increased first-pass puncture success rate combined with comparable procedural duration, which supports the feasibility and safety of ultrasound-guided access in these procedures. Further research directed towards the reduction in access site complications during coronary procedures is warranted and should specifically assess preventive strategies in high bleeding risk patient populations.

Methods

STUDY DESIGN AND OBJECTIVES

The Ultrasound Guided Transfemoral Complex Large-bore PCI Trial (ULTRACOLOR) was an investigator-initiated, international, multicentre study with a prospective, open-label randomised controlled superiority design. Full study rationale, protocol and participating centres have been published previously[12].

The primary objective of this study was to investigate whether the use of ultrasound guidance for TFA with large-bore guide catheters for complex PCI reduces clinically relevant access site-related bleeding or vascular complications.

As secondary objectives, ultrasound-guided and fluoroscopy-guided TFA were compared with regard to procedural duration, first-pass puncture rate, the incidence of accidental venous puncture and VCD failure. Major adverse cardiovascular events (MACE) at discharge and at 1-month follow-up were compared between both randomised groups. Clinically relevant complications of the additional access site (if applicable) were also studied.

TRIAL ORGANISATION

The trial was approved by the appropriate ethics review board at each site. Written informed consent was obtained from all patients before enrolment. The trial was designed in accordance with the Declaration of Helsinki. All data were collected in an electronic data capturing system (eDREAM [Diagram B.V.]). Diagram B.V. was responsible for overall trial and data management, as well as the monitoring of the study. The evaluation of serious adverse events was performed by an independent data safety monitoring board (DSMB). A clinical events committee (CEC) reviewed and adjudicated all endpoint-related adverse events and was blinded to the randomised strategy (see **Supplementary Appendix 1** for the CEC composition and charter). ULTRACOLOR follows the CONSORT guidelines **(Supplementary Appendix 2)** and has been registered at ClinicalTrials.gov: NCT04837404.

SITE SELECTION

All participating centres and operators were selected based on their experience with complex PCI and ultrasound-guided puncture. Every potential site had to fill in a questionnaire about the number and type of complex PCIs performed yearly, the preferred sheath size for complex PCI, and whether ultrasound-guided puncture in complex PCI was

Abbreviations

AE	adverse event
BARC	Bleeding Academic Research Consortium
CEC	clinical events committee
CTO	chronic total occlusion
DSMB	data safety monitoring board
Fr	French
MACE	major adverse cardiovascular events
PCI	percutaneous coronary intervention
TFA	transfemoral access
TRA	transradial access

already standard of care. Furthermore, a detailed step-by-step approach for both access site strategies was provided in the previously published study design paper[12]. All participating operators received these instructions either by onsite training or by using a prerecorded training video.

INCLUSION

Patients of 18 years or older presenting with chronic coronary syndrome, unstable angina or non-ST-segment elevation myocardial infarction and scheduled for PCI of complex coronary lesions, including CTO, left main stem, heavily calcified lesions and complex bifurcations, in whom the operator anticipated the need for at least one 7 Fr guide catheter for TFA, were screened for inclusion. Full definitions of complex coronary lesions have been published previously[12]. Patients with ST-segment elevation myocardial infarction or cardiogenic shock were excluded. Patients with contraindications for large-bore femoral access, such as occlusive peripheral artery disease, were also excluded.

RANDOMISATION

After providing written informed consent, eligible subjects were randomly assigned in a 1:1 ratio to receive one of the two study treatments. Treatment assignments were performed centrally through a dedicated website in random permuted blocks with stratification by site. There was no blinding of the randomisation assignment.

STUDY GROUP DEFINITION

Femoral access was performed according to the randomised strategy.

ULTRASOUND-GUIDED ACCESS GROUP

The course of the femoral artery was first identified by palpation. Additional use of fluoroscopy to identify the femoral head was optional but recommended. Under direct visualisation with ultrasound, local anaesthetics were administered subcutaneously, and a subsequent puncture was performed. The use of micropuncture was optional and according to operators' experience and preference.

FLUOROSCOPY-GUIDED ACCESS GROUP (COMPARATOR)

The course of the femoral artery was first identified by palpation, and additional fluoroscopy was performed to identify the ideal site for local anaesthetics administration and femoral artery puncture. The use of micropuncture was optional and according to operators' experience and preference.

ENDPOINTS

The primary endpoint was defined as clinically relevant access site-related bleeding or vascular complication requiring intervention of the randomised access site during hospitalisation. Bleeding was classified according to the Bleeding Academic Research Consortium (BARC) criteria and considered clinically relevant when the score was 2, 3 or 5[13]. All bleeding, vascular complications and MACE were adjudicated by the CEC. The CEC was blinded to the randomisation group. The severity of bleeding/complication and type of intervention for vascular complications were specified in the CEC manual **(Supplementary Appendix 1)**.

Secondary safety and efficacy endpoints were as follows (see also **Supplementary Appendix 3** for definitions):

- BARC 2, 3 or 5 access site-related bleeding or vascular complication requiring intervention at the primary femoral access site at 30-day follow-up
- BARC 2, 3 or 5 access site-related bleeding or vascular complication requiring intervention at the secondary femoral or radial access site (at discharge and at 30-day follow-up)
- MACE (at discharge and at 30-day follow-up)
- Vascular complication not requiring intervention at the primary femoral access site (at discharge and at 30-day follow-up)
- Vascular complication not requiring intervention at the secondary femoral or radial access site (at discharge and at 30-day follow-up)
- Procedural duration
- Time to access
- First-pass puncture rate
- Number of access attempts
- Accidental venepuncture rate
- Crossover (fluoroscopy-guided to ultrasound-guided or vice versa)
- Suboptimal femoral artery puncture, based on the iliofemoral angiogram[12]
- Extremity pain (measured by the numeric rating scale [NRS]) directly after the procedure, at discharge, and at 30-day follow-up

PROCEDURE, HAEMOSTASIS AND CLINICAL COURSE

The PCI strategy and choice of materials were left to the discretion of the operator. An iliofemoral angiogram was mandated before VCD placement to check for complications and to score the access height. Haemostasis was achieved, according to the local protocol, using a VCD unless contraindicated; in case of the latter, manual compression with a bandage was applied for haemostasis. Failure of VCDs was documented. The pain score related to the primary femoral access site directly after haemostasis was collected according to the NRS. Before discharge, all access sites were checked for potential complications including haematoma (haematoma size was documented). An additional ultrasound was performed within 1 month in case of suspected femoral artery occlusion or other vascular complications of the (additional) femoral or radial artery.

FOLLOW-UP

Follow-up was performed 30 days after index procedure discharge either by a phone call or an outpatient clinic visit. Any MACE, access site bleeding or vascular complications were documented. Adverse events (AE) were monitored from inclusion to 30-day follow-up and assessed by an independent DSMB, composed of two experienced cardiologists and one statistician, who reviewed patient safety and study integrity (see **Supplementary Appendix 4** for the composition and reports of the DSMB).

SAMPLE SIZE CALCULATION AND STATISTICS

The appropriate sample size was estimated at 542 subjects (271 subjects in each group), based on a type 1 error rate of 5% and a power of 80%, assuming a 16% complication rate in the comparator group and a 49% reduction (7.84%

complication rate) in the ultrasound-guided group[3,14]. An intention-to-treat analysis was used for the primary analysis and included all randomised patients. Statistical analysis was performed according to a predefined statistical analysis plan **(Supplementary Appendix 5)** by an independent statistician using SAS statistical software version 9.4 (SAS Institute).

Predefined subgroup analyses were performed including several potential differing treatment effects for several high-risk subgroups. A detailed specification of the subgroups can be found in the statistical analysis plan **(Supplementary Appendix 5)**.

Results

STUDY POPULATION CHARACTERISTICS

From June 2021 to March 2023, 561 patients were screened for inclusion, of which 544 patients were included and randomised to either ultrasound-guided (274 patients) or fluoroscopy-guided (270 patients) large-bore transfemoral access, as represented in the enrolment flow diagram **(Figure 1)**. The median age was 71 years, and 76% were male. The primary indication for complex PCI was stable angina (71%). Most patient characteristics were evenly distributed in both treatment groups **(Table 1)**, except for previous coronary artery bypass grafting (13% in the fluoroscopy-guided and 21% in the ultrasound-guided group; p=0.02).

VASCULAR ACCESS CHARACTERISTICS

The right femoral artery was predominantly used as the primary access site (92%). An additional arterial access site was used in

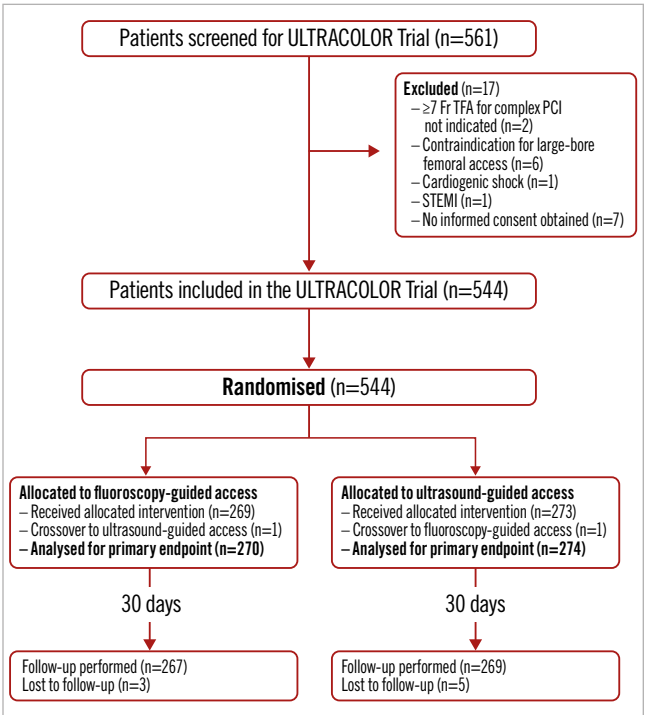


Figure 1. *Enrolment flow diagram for the ULTRACOLOR Trial. PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TFA: transfemoral access*

Table 1. Baseline characteristics.

	Fluoroscopy-guided (n=270)	Ultrasound-guided (n=274)
Age, years	71 [62-77]	72 [64-78]
Male	209 (77)	205 (75)
Height, cm	174 [168-181]	174 [168-179]
Weight, kg	82 [75-93]	83 [73-95]
BMI, kg/m^2	28 [25-30]	28 [25-31]
Medical history		
Hypertension	197 (73)	208 (76)
Hypercholesterolaemia	194 (72)	201 (73)
Diabetes mellitus	80 (30)	78 (28)
Current smoker	47 (17)	48 (18)
Family history of CAD	110 (41)	102 (38)
Peripheral arterial disease	40 (15)	39 (14)
Previous MI	95 (35)	102 (37)
Previous PCI	126 (47)	128 (47)
Previous CABG	36 (13)	58 (21)
Previous stroke	12 (4)	23 (8)
Indication for complex PCI		
Chronic coronary syndrome	239 (88)	236 (86)
Stable angina	188 (70)	196 (72)
Heart failure	12 (4)	11 (4)
Arrhythmia	14 (5)	7 (3)
Other	25 (9)	22 (8)
NSTE-ACS	31 (12)	38 (14)
Left ventricular ejection fraction		
Poor (<30%)	7 (2)	12 (4)
Moderate (30-50%)	71 (26)	81 (30)
Good (>50%)	174 (64)	161 (59)
Unknown	18 (8)	20 (7)
Laboratory results		
Hb, mmol/l	8.7 [8.0-9.4]	8.7 [8.1-9.2]
MDRD, ml/min/1.73 m^2	77 [61-88]	71 [58-83]
Thrombocytes, x10^9	229 [184-272]	233 [191-278]
Reason for large-bore femoral access		
Radial artery(ies) too small	24 (9)	25 (9)
Radial artery(ies) occluded/ not palpable	2 (1)	3 (1)
Double radial access was not standard practice for hybrid CTO	136 (51)	133 (49)
Operator preference	88 (32)	81 (30)
Patient preference	11 (4)	19 (6)
Previous radial access issues	9 (3)	13 (5)

Data are presented as n (%) or median [IQR]. BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; cm: centimetres; kg: kilograms; CTO: chronic total occlusion; Hb: haemoglobin; IQR: interquartile range; m: metres; MI: myocardial infarction; MDRD: Modification of Diet in Renal Disease; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention

56% of patients, of whom 21% had femoral and 79% radial secondary access. One patient in each group (<1%) crossed over to the other randomised strategy. Micropuncture was used in <1% of patients. The first-pass puncture success rate was higher in the ultrasound-guided group (92% vs 85%; p=0.02) **(Central illustration)**. The median number of attempts was 1 in each group (interquartile range [IQR] 1-1). The median time to access was 60 seconds (IQR 60-135) for ultrasound-guided access and 60 seconds (IQR 60-150) for fluoroscopy-guided access. A high puncture occurred significantly more often in the ultrasound-guided access group (5% vs 1%; p=0.03), while a low puncture occurred more often in the fluoroscopy-guided group (10% vs 5%; p=0.02). Accidental venepuncture occurred in 4% of patients with fluoroscopy-guided access versus 2% with ultrasound-guided access (p=0.18). The Angio-Seal (Terumo) VCD was the most applied haemostasis technique in both randomisation groups, and its use was evenly distributed (fluoroscopy 82% vs ultrasound 81%). VCD failure occurred in 6% of the fluoroscopy-guided procedures and in 5% of the ultrasound-guided procedures (p=0.67). The median NRS for access site pain was 0 in both groups. A complete overview of access site characteristics is represented in **Table 2**.

LESION AND PROCEDURAL CHARACTERISTICS

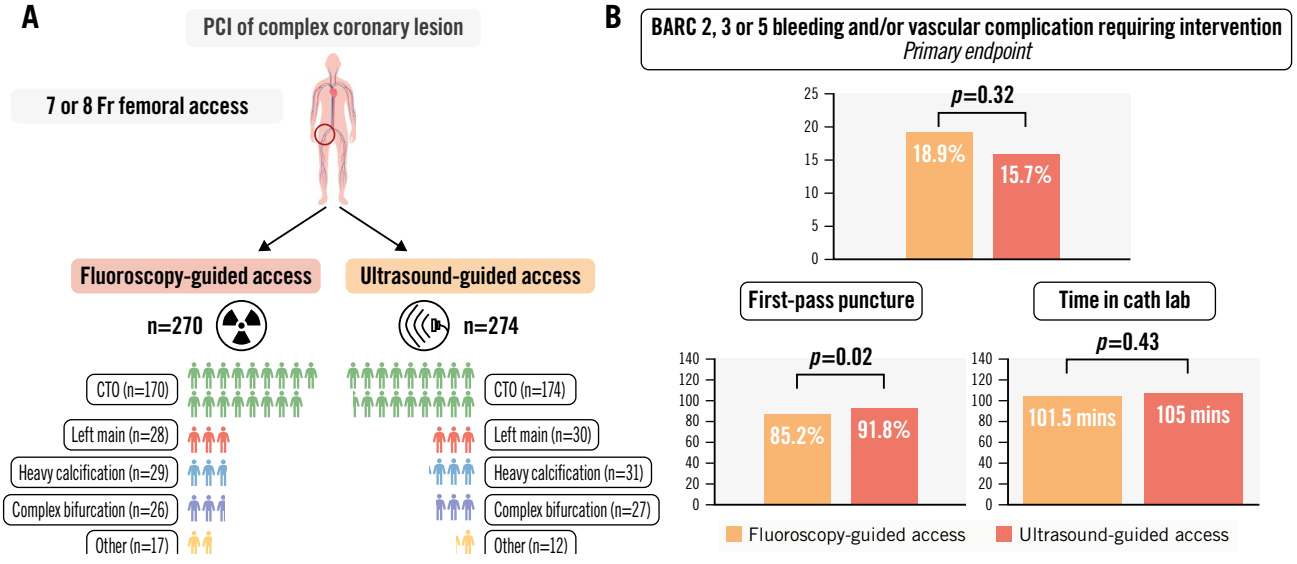
CTO was the most frequent type of complex coronary lesion (63%), followed by heavy calcification (11%), left main stem (11%) and complex bifurcation (10%). The types of complex coronary lesions were evenly distributed between study groups **(Table 3)**. The same applies for the CTO lesion complexities (median Japanese CTO [J-CTO] score 2.0 [IQR 1-3]), left main lesions and complex bifurcation lesions. The other angiographic characteristics were also evenly distributed **(Supplementary Table 1)**. The median procedural duration was 75 minutes (IQR 55-120) for ultrasound-guided access and 75 minutes (IQR 50-120) for fluoroscopy-guided access. The total time in the catheterisation laboratory was 105 minutes (IQR 75-150) for ultrasound-guided access and 102 minutes (IQR 74-148) for fluoroscopy-guided access (p=0.43). Angiographic success was achieved in 94% of patients. The success rates for patients with CTO PCI and non-CTO complex PCI were 91% and 99%, respectively. No difference was observed between the two randomised strategies regarding procedural success. During the procedure, clopidogrel was the most common $P2Y_{12}$ inhibitor (82%), and 6% had uninterrupted vitamin K antagonist or direct oral anticoagulant therapy. Anticoagulant use and activated clotting time (ACT) levels were comparable between both groups **(Supplementary Table 2)**.

CLINICAL OUTCOME AT DISCHARGE

At discharge, the occurrence of the primary endpoint was 15.7% in the ultrasound-guided group versus 18.9% in the fluoroscopy-guided group (p=0.32). The individual components of the primary endpoint were not significantly different between both groups, and the same applies for BARC 1 bleeding (15% for fluoroscopy-guided vs 17% for ultrasound-guided; p=0.53). The occurrence of MACE during hospitalisation was 3% in the fluoroscopy-guided group and 1% in the ultrasound-guided group (p=0.14). Secondary access site-related BARC 2, 3 or 5 bleeding or vascular complications requiring intervention occurred in 2% of the fluoroscopy-guided group and 4% of the

EuroIntervention — Central **Illustration**

Outcomes of patients undergoing fluoroscopy-guided or ultrasound-guided large-bore femoral access in complex PCI – the ULTRACOLOR Trial.



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A) Patient characteristics after randomisation. B) Main outcomes. BARC: Bleeding Academic Research Consortium; cath lab: catheterisation laboratory; CTO: chronic total occlusion; mins: minutes; PCI: percutaneous coronary intervention

Table 2. Access site characteristics.

	Fluoroscopy-guided (n=270)	Ultrasound-guided (n=274)	*p*-value
Site of femoral access			0.02
Right	255 (94)	244 (89)	
Left	15 (6)	30 (11)	
Crossover	1 (<1)	1 (<1)	0.99
Sheath size for primary access			0.74
7 Fr	230 (85)	236 (86)	
8 Fr	40 (15)	38 (14)	
Secondary access site used	145 (54)	161 (59)	0.25
Radial	126 (87)	117 (73)	0.002
Femoral	19 (13)	44 (27)	0.002
Sheath size for secondary access			0.63
≤6 Fr	59 (41)	70 (44)	
7 Fr	85 (58)	89 (55)	
8 Fr	1 (<1)	2 (1)	
Micropuncture technique	1 (<1)	2 (<1)	1.00
First-pass puncture	230 (85)	251 (92)	0.02
Accidental venous puncture	10 (4)	5 (2)	0.18
Number of attempts	1 [1-1]	1 [1-1]	0.19
Time to access, secs	60 [60-150]	60 [60-135]	0.86
Puncture height			
Low	27 (10)	13 (5)	0.02
Middle	194 (72)	204 (74)	0.45
High-middle	45 (17)	43 (16)	0.77
High	4 (1)	13 (5)	0.03
No iliofemoral angiography performed	0	1 (<1)	
Haemostasis technique			0.54
Angio-Seal VCD	221 (82)	222 (81)	
Other VCD	23 (8)	30 (11)	
Manual compression	26 (10)	23 (8)	
Reason not to use VCD			
Calcifications	12 (46)	10 (44)	0.63
Possible complication	5 (19)	4 (17)	0.72
Bleeding	2 (8)	3 (13)	0.67
Low puncture	7 (27)	6 (26)	0.75
Primary closure technique failure*	17 (6)	15 (5)	0.67

Data are presented as n (%) or median [IQR]. *See **Supplementary Appendix 2** for definition. Fr: French; IQR: interquartile range; secs: seconds; VCD: vascular closure device

Table 3. Lesion and procedural characteristics.

	Fluoroscopy-guided (n=270)	Ultrasound-guided (n=274)	*p*-value
Lesion type			
CTO	170 (63)	174 (64)	0.85
J-CTO score	2 [1-3]	2 [1-3]	0.42
Left main stem	28 (10)	30 (11)	0.89
Heavy calcification	29 (11)	31 (11)	0.90
Complex bifurcation	26 (10)	27 (10)	0.99
Other complex lesion	2 (1)	2 (1)	0.76
No PCI performed	15 (5)	10 (3)	0.29
Angiographic success	243 (95)	245 (93)	0.23
Haemodynamic mechanical support used	1 (<1)	2 (1)	0.75
Impella	1 (<1)	1 (<1)	
ECLS	0	0	
IABP	0	1 (<1)	
Procedural duration, mins*	75 [50-120]	75 [55-120]	0.44
Total time in cath lab, mins*	102 [74-148]	105 [75-150]	0.43

Data are presented as n (%) or median [IQR]. *See **Supplementary Appendix 2** for definition. CTO: chronic total occlusion; ECLS: extracorporeal life support; IABP: intra-aortic balloon pump; IQR: interquartile range; J-CTO: Japanese chronic total occlusion; mins: minutes

ultrasound-guided group (p=0.34). Vascular complications not requiring intervention were also comparable for both primary and secondary access sites (respectively, 0% and 0% for fluoroscopy-guided access, and 0.7% and 0% for ultrasound-guided access). The clinical outcome parameters at discharge are displayed in **Table 4**. Delayed discharge (21.0% for fluoroscopy-guided and 21.5% for ultrasound-guided access; p=0.91) and additional imaging of the access site (11% vs 9%; p=0.60) were comparable for both groups (see **Supplementary Table 3** for details). The median NRS score for primary access site pain at discharge was 0 for both randomised strategies. No significant interaction with the primary outcome was observed for the prespecified subgroups **(Figure 2)**.

FOLLOW-UP OUTCOMES

Follow-up was completed in 99% of patients with a median follow-up duration of 32 days. The occurrence of primary access site BARC 2, 3 or 5 bleeding or vascular complications requiring intervention at follow-up did not show a statistically significant difference between the fluoroscopy-guided and ultrasound-guided group (21% vs 16%; p=0.19). The MACE rate at follow-up was 4% in the fluoroscopy-guided group and 3% in the ultrasound-guided group (p=0.32). The median NRS for access site pain was 0 in both groups. Further specification of the clinical outcome at 30-day follow-up is presented in **Table 5**. No significant interaction with the primary outcome was observed for the prespecified subgroups at 30-day follow-up **(Supplementary Figure 1)**.

Discussion

ULTRACOLOR is the first randomised controlled trial (RCT) comparing ultrasound-guided with fluoroscopy-guided large-bore TFA for PCI of complex coronary lesions, including a large subset of CTO lesions. In the current trial, ultrasound-guided puncture did not significantly reduce clinically relevant

Table 4. Clinical outcome during hospitalisation.

	Fluoroscopy-guided (n=270)	Ultrasound-guided (n=274)	*p*-value
Primary access site BARC 2, 3 or 5 bleeding or vascular complication requiring intervention	51 (18.9)	43 (15.7)	0.32
Any primary access site bleeding	90 (33)	90 (33)	0.83
BARC 1	41 (15)	47 (17)	0.53
BARC 2	43 (16)	34 (12)	0.24
BARC 3	6 (2)	9 (3)	0.44
BARC 5	0	0	
Primary access site vascular complication requiring intervention	6 (2)	4 (1)	0.54
Primary access site pain (NRS)	0 [0-0]	0 [0-0]	0.85
Secondary access site BARC 2, 3 or 5 bleeding or vascular complication requiring intervention	3 (2)	7 (4)	0.34
MACE	8 (3)	3 (1)	0.14
Death (all causes)*	0	1 (<1)	1.00
MI*	8 (3)	2 (1)	0.06
Repeated revascularisation*	0	0	

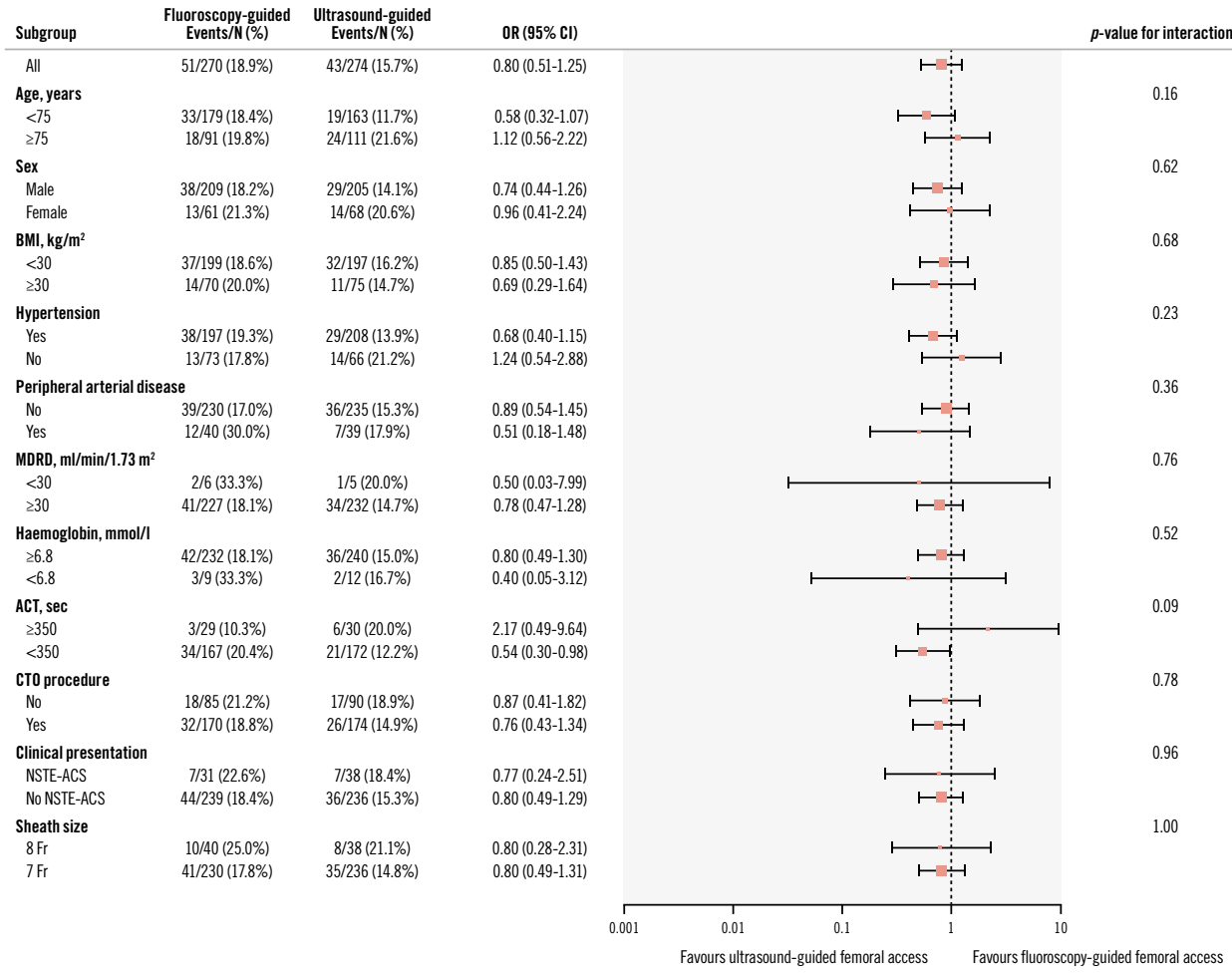
Data are presented as n (%) or median [IQR].*Hierarchical representation of individual MACE components. BARC: Bleeding Academic Research Consortium; IQR: interquartile range; MACE: major adverse cardiovascular events; MI: myocardial infarction; NRS: numeric rating scale

bleeding and vascular complications. The same applies for the secondary safety outcomes, including MACE. However, ultrasound-guided access resulted in increased first-pass puncture success. Overall, our results are in line with recent RCTs, albeit with standard sheath sizes and less complex lesions. The UNIVERSAL RCT demonstrated no significant benefit in clinically relevant bleeding for ultrasound-guided access compared to fluoroscopy-guided access, but it showed improved first-pass puncture success for ultrasound-guided access[11]. Other recent RCTs showed similar results. This includes a trial by Marquis-Gravel et al which randomised 129 patients requiring TFA to either ultrasound-guided access or landmark-guided access and showed no benefit in significant bleeding[15]. The Standard versus Ultrasound-guided Radial and Femoral access in coronary angiography and intervention (SURF) trial by Nguyen et al also did not demonstrate a benefit in major bleeding or MACE, but once again, higher first-pass puncture success and a lower number of attempts for ultrasound-guided access were seen[16]. Recently, two meta-analyses were published regarding ultrasound-guided versus non-ultrasound-guided femoral puncture in coronary procedures. Both incorporated the same nine trials. The individual patient data meta-analysis by d'Entremont et al demonstrated a significant reduction of access site complications in ultrasound-guided access[17]. However, the incidence of their primary endpoint was mainly driven by large haematomas, which are not associated with increased mortality[18]. The occurrence of clinically relevant BARC 2 and 3 bleeding events was not significantly lower when ultrasound was used, as was also demonstrated by the meta-analysis incorporated in the UNIVERSAL trial publication[11]. In addition, no benefit of ultrasound could be demonstrated in a subgroup analysis of ≥7 versus <7 Fr access in the meta-analysis by d'Entremont et al, although large-bore access was used in only 7.9% of patients[19]. These findings are in line with the results of the current trial.

The overall femoral access site complication rate in the current trial was 17.3%, which is slightly lower compared to the Complex Large-bore Radial PCI Trial (COLOR)[3]. COLOR compared 7 Fr TFA with 7 Fr TRA in a similar study population and showed a 19.1% occurrence of the primary endpoint in TFA patients. One explanation may be the mandatory use of fluoroscopy-guided puncture in the control group of the current trial, which may help to prevent some bleeding and vascular complications. Compared to classical anatomical landmark-guided puncture, fluoroscopy-guided femoral access may reduce the incidence of bleeding and vascular complications[20-22]. The increased experience and proficiency of complex PCI operators with both fluoroscopy-guided and ultrasound-guided femoral artery puncture, supported by the step-by-step manual and training provided to all participating centres, may be another explanation for the slightly lower event rate. The UNIVERSAL trial demonstrated an event rate of 14.5% for their primary endpoint, which is slightly lower than the endpoint of the current trial. This can be attributed to the large proportion of standard-sized sheaths (<7 Fr sheaths were used in 81% of patients) in that trial. Of note, the primary endpoint definition of the UNIVERSAL trial was slightly different from that of the current trial, with the additional inclusion of large haematomas.

The rationale for using ultrasound-guided puncture is to avoid a suboptimal puncture height and puncture in calcified plaques, which are both associated with higher complication rates and failure of VCDs. We were able to observe that sheath placement below the femoral bifurcation occurred significantly less often with ultrasound-guided access, which makes sense as the femoral bifurcation can be directly visualised by ultrasound. However, high sheath placement (above the internal epigastric artery [IEA]) paradoxically occurred more often in the ultrasound-guided group. This may be explained by the fact that the IEA is not easy to visualise with ultrasound, and efforts to avoid a low puncture and/or puncture in a calcified plaque may therefore result in a (too) high puncture. Operators should be aware of this, since a high puncture may increase the risk for retroperitoneal haematoma[10]. When using ultrasound to select the optimal puncture location, the standard application of both transversal and longitudinal views may reduce the occurrence of an inadvertent high puncture. Of note, in the current trial, a high puncture location did not result in an increased rate of major bleeding or vascular complications.

When a VCD is used for arterial haemostasis, ultrasound-guided puncture may theoretically lower the risk of VCD failure caused by puncture in a calcified plaque or below the femoral bifurcation. A subanalysis of the UNIVERSAL trial was performed for patients in whom haemostasis was achieved using



* *p*-value is the test of interaction between treatment and each subgroup unadjusted for multiplicity.

Figure 2. *Subgroup analyses at discharge. ACT: activated clotting time; BMI: body mass index; CI: confidence interval, CTO: chronic total occlusion; MDRD: Modification of Diet in Renal Disease; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; OR: odds ratio*

Table 5. Clinical outcome at follow-up.

	Fluoroscopy-guided (n=270)	Ultrasound-guided (n=274)	*p*-value
Follow-up performed	267 (99)	269 (98)	0.49
Time to follow-up, days	32 [29-36]	32 [29-36]	0.55
Primary access site BARC 2, 3 or 5 bleeding or vascular complication requiring intervention	55 (21)	44 (16)	0.19
Any primary access site bleeding	98 (36)	94 (34)	0.69
BARC 1	45 (17)	51 (19)	0.55
BARC 2	45 (17)	34 (13)	0.16
BARC 3	8 (3)	9 (3)	0.83
BARC 5	0	0	
Primary access site vascular complication requiring intervention	7 (3)	6 (2)	0.76
Secondary access site BARC 2, 3 or 5 bleeding or vascular complication requiring intervention	3 (2)	7 (4)	0.34
MACE	11 (4)	7 (3)	0.32
Death (all causes)*	2 (1)	2 (1)	1.0
MI*	9 (3)	5 (2)	0.27
Repeated revascularisation*	0	0	

Data are presented as n (%) or median [IQR].*Hierarchical representation of individual MACE components. BARC: Bleeding Academic Research Consortium; IQR: interquartile range; MACE: major adverse cardiovascular events; MI: myocardial infarction

a VCD (53% of the trial population)[19]. In this subgroup, access site complications were significantly lower when ultrasound-guided access was used. In the current trial, VCD use was high (91%), and no benefit was demonstrated for patients treated with a VCD, possibly because of the low number of patients not receiving a VCD. Primary closure device failure did not differ between the two randomised groups and occurred in 5.9% of the total study population. This is only slightly higher than the 5.3% observed in the Instrumental Sealing of Arterial Puncture Site Closure Device Versus Manual Compression Trial (ISAR-CLOSURE), where 6 Fr sheaths were used, but lower than in the UNIVERSAL trial subanalysis (8.1%) which used 6 Fr sheaths in the majority of patients as well[11,23].

Other prespecified analyses for a number of subgroups with known high bleeding risk did not show significant interaction with the primary endpoint; this was also probably hindered by small sample sizes. For example, the proportion of patients with obesity (defined as a body mass index [BMI] ≥30) was 27%, which is relatively low when compared to similar trials (41% in the UNIVERSAL trial). In these patients, a correct puncture position as well as haemostasis without the use of ultrasound can be difficult because of the deeper location of the femoral artery. It should therefore be highlighted that for individual cases with high bleeding risk factors, including acute coronary syndrome, obesity, peripheral artery disease, renal insufficiency and female sex, ultrasound-guided femoral access should still be encouraged[17,24]. Future studies focusing on high bleeding risk patients would be relevant and probably require smaller sample sizes to demonstrate the potential benefit of ultrasound guidance, especially with large-bore access. The use of 8 Fr guide catheters in the current study was relatively low (15%), which reflects daily practice as 7 Fr access is usually sufficient to accommodate most (simultaneous) equipment for complex PCI. Whether or not ultrasound guidance has benefits in 8 Fr, or even larger-bore, access, for example, in case of mechanical circulatory support device use (13 Fr to 23 Fr sheath size) or transcatheter aortic valve replacement (14 Fr to 20 Fr sheath size), should be investigated in future RCTs.

Current European and American guidelines on myocardial revascularisation do not specifically address or endorse ultrasound-guided femoral access for coronary angiography and/or PCI[25,26]. In our study, even though ultrasound-guided large-bore TFA in complex PCI did not show a significant benefit in clinically relevant access site complications, we found it to be safe and associated with increased first-pass puncture success rates, without any increase in procedural time. As such, its use may still be considered or even encouraged, especially in high bleeding risk patients and for operators inexperienced in femoral access.

Limitations

First, blinding of the randomised strategy to the operator was not possible for obvious reasons, introducing a chance for selection bias. However, all safety endpoints were adjudicated by an independent and blinded CEC.

Second, in a significant proportion of patients, a secondary access site was used, which may have influenced the safety outcomes. However, use of a secondary access was evenly distributed between the two groups, and the primary outcome was dependent solely on the primary access site, which was subject to the randomised strategy.

Third, in this trial the true effect size turned out to be lower than the anticipated 49%, and therefore, it may be underpowered to detect a smaller relative risk reduction for ultrasound-guided puncture with regard to relevant access site-related complications. In addition, the subgroup analyses were hampered by the low sample size.

Fourth, the use of micropuncture was very low in this trial, as it is not common practice in the participating centres. Scarce and conflicting evidence exists about the effect on access site complications when using the micropuncture technique[27-29].

Fifth, experience and proficiency with using ultrasound may vary among different centres and operators. However, all participating centres and operators were selected based on their experience with complex PCI and access site management, and a step-by-step manual as well as onsite or video training was supplied.

Finally, because of technical issues with simultaneous inclusion in multiple sites, two extra patients were randomised after the official randomisation process was closed. This has been reported to the medical ethics committee and DSMB **(Supplementary Appendix 3)**.

Conclusions

As compared to fluoroscopy guidance, the routine use of ultrasound guidance for large-bore transfemoral access in complex PCI did not reduce clinically relevant bleeding or vascular complications, although it did increase first-pass puncture success. In addition, the crossover rate was very low, and the total time in the catheterisation laboratory and time to access were both comparable, underlining the applicability of ultrasound-guided access in these patients.

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Conflict of interest statement

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Supplementary data

Supplementary Appendix 1. Clinical events committee composition and charter.
Supplementary Appendix 2. CONSORT checklist.
Supplementary Appendix 3. Definitions.
Supplementary Appendix 4. Composition and safety reviews of the DSMB.
Supplementary Appendix 5. Statistical analysis plan.
Supplementary Table 1. Lesion and procedural characteristics.
Supplementary Table 2. Antiplatelet and anticoagulant therapy.
Supplementary Table 3. Hospital stay and access site imaging.
Supplementary Figure 1. Subgroup analysis at 30-day follow-up.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00089

Supplementary data

Supplementary Appendix 1. Clinical events committee composition and charter.

ULTRASOUND GUIDED **TRA**NSFEMORAL **CO**MPLEX **L**ARGE-B**OR**E PCI TRIAL
Randomized trial
Study design

The ULTRACOLOR trial is a prospective, randomized clinical trial.
Patients are eligible for study participation when complex PCI is indicated requiring 7 or more French sheath and guiding catheters with at least one planned femoral access site according to the operator. If patients comply with inclusion and exclusion criteria and provide written informed consent they will be randomized in a 1:1 fashion between the two study treatments, ultrasound guided large-bore femoral access or fluoroscopy guided access.
The primary objective is to investigate if ultrasound guided femoral access is associated with less clinically relevant access site related bleeding and/or vascular complications requiring intervention as compared to the fluoroscopy guided method for complex PCI with large-bore access.
Primary endpoint is defined as:
- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the primary femoral access site during index hospitalization (see **Supplementary Appendix 2** for definitions of primary and secondary access site).
The secondary endpoint is defined as:
- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the secondary femoral or radial access site during index hospitalization.
- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the primary femoral access site at 1 month
- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the secondary femoral or radial access site at1 month
- MACE (hospitalization and 1 month)
- Procedural duration
- First pass puncture
- Number of access attempts
- Accidental venipuncture
- Access below the femoral artery bifurcation (ileofemoral angiogram)
- Vascular complication not requiring intervention of the primary femoral access site (hospitalization and 1 month)
- Vascular complication not requiring intervention of the secondary femoral or radial access site (hospitalization and 1 month)

Purpose of the CEC
Adjudication of clinical events by an independent committee, i.e. the Clinical Event Committee (CEC), is critical to ensure high quality data in a clinical trial. The CEC provides medical review of study endpoints. Events are identified through programmed queries based on triggers from the case report forms and other study data.
The CEC is composed of individuals who are experts in operational and medical aspects and are not affiliated with the study. The members of the CEC for the ULTRACOLOR trial are listed in the table at page 3.

The purpose of the CEC is to provide an objective, unbiased review of the clinical data and supporting source documentation. Members of the CEC are provided with data summaries from the clinical study in a blinded fashion without identification of patient.

Responsibilities of the CEC members

The CEC members are responsible for reviewing each event as defined in the protocol. Their work is independent and impartial.

The CEC member will;

- Attend at the Clinical Events Committee meeting
- Approve the Clinical Events Committee Guidelines in order to classify the events
- Review and adjudicate all clinical endpoints as reported by investigators during the study.

Review of End Points

All clinical endpoints:

Primary endpoint:

- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the primary femoral access site during index hospitalization.

Secondary endpoints:

- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the secondary femoral or radial access site during index hospitalization.
- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the primary femoral access site at 1 month
- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the secondary femoral or radial access site at1 month
- MACE (hospitalization and 1 month)
- Procedural duration
- First pass puncture
- Number of access attempts
- Accidental venipuncture
- Access below the femoral artery bifurcation (ileofemoral angiogram)
- Vascular complication not requiring intervention of the primary femoral access site (hospitalization and 1 month)
- Vascular complication not requiring intervention of the secondary femoral or radial access site (hospitalization and 1 month)

Meeting schedule and organization of the meetings

Enrolment in the ULTRACOLOR trial started in June 2021. CEC meetings will be held 2-4 weeks prior to each Data Safety Monitoring Board (DSMB) meeting. DSMB meetings are planned for every 125 patients that are included in the study or yearly (whatever comes first). The meetings will be planned by Diagram B.V. with the CEC members.

Procedure for adjudicating events

All information provided to the CEC will be in a blinded fashion without identification information of patients and randomized strategy.

The clinical endpoints will be adjudicated by two CEC members according to the definitions stated in **Supplementary Appendix 2.**

When two members reach consensus about the adjudication of the event, the adjudication is final. In the case consensus is not met, the third member of the CEC will review the event and make the final adjudication.

All communication with the CEC must be considered privileged information. After each meeting Diagram B.V. will prepare a status report for the Sponsor.

Role of the CEC chairman

The CEC chairman is the person who presides over the Adjudication Committee and procedures. The chairman is also requested to deal with situations of disagreement or situations where the charter remains inconclusive.

CEC members:

Dr. E. McFadden (Chairman), Cork University Hospital, Cork, Ireland

Dr. J. Wykrzykowska, UMCG, Groningen, The Netherlands

Dr. W. den Dekker, Erasmus MC, Rotterdam, The Netherlands

Necessary documentation to assess the endpoints and events:

- CRF information
- Autopsy report
- Discharge letter of baseline (and event)
- Event coronary angiogram and PCI
- Event ECG
- Baseline and Event coronary angiogram (and PCI (CD-rom))
- Cathlab/surgery report
- Laboratory results
- Death certificate/ autopsy/pathology report

Definitions

1 Bleeding

The CEC will adjudicate all cases of bleeding according to the Bleeding Academic Research Consortium definition[35]**.**

Type 0: no evidence of bleeding.

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional. Examples include, but are not limited to, bruising, hematoma, nosebleeds, or hemorrhoidal bleeding for which the patient does not seek medical attention. Type 1 bleeding may include episodes that

lead to discontinuation of medications by the patient because of bleeding without visiting a healthcare provider.

Type 2: any clinically overt sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) BARC bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: First, it requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. Examples include, but are not limited to, coiling, compression, use of reversal agents (eg, vitamin K, protamine), local injections to reduce oozing, or a temporary/permanent cessation of antiplatelet, antithrombin, or fibrinolytic therapy. Second, the bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. Or third, the bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). Examples include, but are not limited to, hematocrit testing, hemoccult testing, endoscopy,
colonoscopy, computed tomography scanning, or urinalysis. A visit or phone call to a healthcare professional during which neither testing nor treatment is undertaken does not constitute type 2 bleeding.

Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:
Any transfusion with overt bleeding

- Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL (provided hemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.

Bleeding Academic Research Consortium type 3b bleeding:

- Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive drugs
  Bleeding Academic Research Consortium type 3c bleeding
- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
- Intraocular bleed compromising vision

Type 4: Coronary Artery Bypass Graft–related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation after closure of sternotomy for the purpose of controlling bleeding

- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
- Chest tube output ≥2 L within a 24-hour period
- Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

Type 5: Fatal bleeding

Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC fatal bleeding is categorized as either definite or probable as follows:
Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy.

The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other.

Bleeding Academic Research Consortium fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed. Bleeding that is contributory but not directly causal to death is not classified as fatal bleeding but may be categorized as other forms of bleeding. Bleeding that leads to cessation of antithrombotic or other therapies may be contributory but again would not be classified as fatal bleeding. Bleeding associated with trauma or with surgery may be fatal, depending on whether it was determined to be directly causal or not.

Agreement Dr. Mc Fadden and Dr. Wykrzykowska from CEC on 15 May 2023:

If hematomas are classified as BARC type 0 by the site (small hematoma, no action/treatment needed), these hematomas will be re-classified as BARC type 1 as bleeding where no action was taken.

2. Vascular complications

The CEC will adjudicate all cases of vascular complications requiring intervention.

¬ **Specified in paragraph 2.1**
2.1. Vascular complication femoral access

Vascular complications requiring intervention: percutaneous, surgical, medical

¬ Retroperitoneal hematoma (i.e. coiling, surgery)
¬ (pseudo) aneurysm (i.e. compression therapy, thrombin injection) ¬ Infection (i.e. antibiotics)
¬ Arteriovenous fistula (i.e. percutaneous or surgical intervention)

¬ Femoral artery occlusion or severe stenosis (percutaneous or surgical intervention)

¬ Dissection (i.e. percutaneous or surgical intervention)
¬ Compartment syndrome (i.e. percutaneous or surgical intervention) ¬ Perforation (i.e. percutaneous, surgical or medical intervention)

2.3 Relation to access site

Access related vascular complications is defined as any vascular complication from site of puncture up to the coronary artery.

3. Death (ARC 2)

The CEC will adjudicate all subject deaths divided into the following categories:

Cardiovascular death is defined as death resulting from cardiovascular causes. The following categories may be collected:

1. Death caused by acute MI
2. Death caused by sudden cardiac, including unwitnessed, death 3. Death resulting from heart failure
4. Death caused by stroke
5. Death caused by cardiovascular procedures
6. Death resulting from cardiovascular hemorrhage
7. Death resulting from other cardiovascular cause

Noncardiovascular death is defined as any death that is not thought to be the result of a cardiovascular cause. The following categories may be collected:

1. Death resulting from malignancy
2. Death resulting from pulmonary causes
3. Death caused by infection (includes sepsis) 4. Death resulting from gastrointestinal causes
5. Death resulting from accident/trauma

6. Death caused by other noncardiovascular organ failure 7. Death resulting from other noncardiovascular cause

Undetermined cause of death is defined as a death not attributable to any other category because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for end point determination.

4. Myocardial infarction

The CEC will adjudicate all cases of MI according to the below mentioned definitions. If an angiogram is available for these events, it will be analyzed by the CEC.

4.1 Third Universal definition of MI

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial

ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

• Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia.
- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

• Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

• Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

• Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
• Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Universal classification of myocardial infarction[36]

Type 1*: Spontaneous myocardial infarction*
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2*: Myocardial infarction secondary to an ischemic imbalance*
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or
demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension,
and hypertension with or without LVH.
Type 3*: Myocardial infarction resulting in death when biomarker values are unavailable*
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood

samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type 4a*: Myocardial infarction related to percutaneous coronary intervention (PCI)*
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia.

Type 4b*: Myocardial infarction related to stent thrombosis*
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/
or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 4c: Myocardial infarction related to restenosis
Myocardial infarction associated with restenosis is characterized by a ≥ 50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values > 99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (< 50%).
Type 5*: Myocardial infarction related to coronary artery bypass grafting (CABG)*
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal
baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new
native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

4.2 **SCAI definition of clinically relevant MI after both PCI and CABG procedures[37].**

1. Patients with normal baseline CK-MB
    - o Peak CK-MB within 48 hours of the procedure ³ 10 times the local laboratory ULN **or**
      Peak CK-MB within 48 hours of the procedure ³ 5 times the local laboratory ULN with new pathologic Q-waves in ³ 2 contiguous leads or new persistent LBBB.
    - o In the absence of CK-MB measurements and a normal baseline cTn; cTn (I or T) level measured within 48 hours of the PCI ³ 70x the local laboratory ULN **or** cTn (I or T)
      level measured within 48 hours of the PCI ³ 35x the local laboratory ULN with new pathologic Q-waves in ³ 2 contiguous leads or new persistent LBBB.
2. Patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling.

o CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

3. Patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels kave not been shown to be stable or falling.

o CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

5. Revascularization

5.1 Location of Revascularization

The location of revascularizations will be adjudicated per the Academic Research Consortium (ARC) definition[37].

- Target Lesion Revascularization (TLR): TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

- Target Vessel Revascularization (TVR): TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion which includes upstream and downstream branches and the target lesion itself
- Non-Target Lesion Revascularization (Non-TLR): Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.
- Non-Target Vessel Revascularization (Non-TVR): Revascularization of the vessel identified and treated as the non-target vessel at the time of the index procedure.

5.2 Urgency

Urgent PCI is defined as PCI at any time indicated for worsening ischemia, ventricular arrhythmias, hemodynamic instability or recurrent ST elevations.
Urgent CABG is defined as non-planned CABG during the same admission.

6. Stent thrombosis

The CEC will adjudicate all cases of stent thromboses (definite, probable or possible according to ARC definitions) for confirmation. If an angiogram is available for these events, it will be evaluated by the CEC. The CEC will also indicate if the stent thrombosis is related to the target vessel.

• Definite or confirmed stent thrombosis: symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis
• Probable stent thrombosis: unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of stent thrombosis

• Possible stent thrombosis: any unexplained death after 30 days

Based on the elapsed time since stent implantation stent thrombosis can be classified as:

- Early (0-30 days post stent implantation) o acute (<24 hours)

o subacute (1-30 days) •Late (>30 days)

Supplementary Appendix 2. CONSORT checklist.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5, 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	10
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10-12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-16
Other information			

Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	Design paper
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

Supplementary Appendix 3. Definitions.

Primary access site: the large bore femoral access site which was subject to the randomized strategy. In case of dual arterial access for CTO PCI, the primary access site is used for cannulation of the target (CTO) vessel. The secondary access site is then used for retrograde visualisation or attempt, and may be < 7 French depending on retrograde options and operators preference.

Safety endpoints: any access site or non accesss site related bleeding or vascular complication, myocardial infarction, death, stroke

Suboptimal femoral sheath placement: sheath placement below the femoral bifurcation or above the origin of the internal epigastric artery as visualized by the obligatory iliofemoral angiogram.

Final activated clotting time (ACT): measured ACT right before sheath removal/start of hemostasis.

MACE: composite of death, myocardial infarction and repeat revascularization

Procedural duration: time from puncture to hemostasis

Time to access: time from local anesthesia to successful sheath placement

First pass puncture: successful puncture of the femoral artery without withdrawing the needle

Cross-over: change from randomized strategy to the other strategy (i.e. ultrasound to fluoroscopy guided puncture and vice versa. Cross-over from femoral to other femoral or femoral to radial access is not defined as cross-over.

Acute coronary syndrome: NSTE-ACS or unstable angina

Chronic coronary syndrome: signs or symptoms of coronary insufficiency without presence of acute coronary syndrome.

Procedural duration: puncture to end procedure

Total time in cathlab: enter cathlab-room to exit room

Other hemodynamic support: consisted only of inotropic agents

Other closure device: Proglide, Perclose, Femoseal

Primary closure device failure: No complete hemostasis achieved with selected vascular closure device.

Supplementary Appendix 4. Composition and safety reviews of the DSMB.

DSMB members: Prof. Dr. Jan G.P. Tijssen (member), Prof. Dr. Jan J. Piek (member), Prof. Dr. Freek W.A. Verheugt (Chair)

DSMB safety reviews:

The DSMB of the ULTRACOLOR trial met July 26, 2022.

The DSMB took notice of the high number of SAEs (87 out of 292 reported adverse events)

The DSMB reviewed 30 day events of BARC 2,3 and 5 bleeding as well as mortality, vascular interventions, myocardial infarctions, revascularisations and stent thromboses in the 250 patients randomized so far.

The consensus is that the trial can be continued as planned

The DSMB of the ULTRACOLOR trial met April 4, 2023.

The DSMB reviewed the in-hospital and 30 day events of BARC 2,3 and 5 bleeding as well as mortality, access complications, vascular interventions, myocardial infarction, revascularisations and stent thrombosis in the 481 patients (88% of the 544 patients randomized so far).

The consensus is that the trial can be continued as planned.

The DSMB considers this meeting as the final one.

The DSMB of the ULTRACOLOR trial met April 24, 2023.

The DSMB discussed an issue in the trial, that 2 patients (one in Belgium and one in Germany) had been randomized after the official randomization process had been closed. The consensus is that these 2 patients should be included in the final analysis. Furthermore, the METCs should be informed about this problem, which is not considered as a major protocol violation. Finally, the trial insurance authorities must be informed about it, also those in Germany and Belgium.

The DSMB will share the final results of the trial with the Steering Committee, about six weeks before the presentation.

Supplementary Appendix 5. Statistical analysis plan.

STATISTICAL ANALYSIS PLAN

ULTRASOUND GUIDED TRANSFEMORAL COMPLEX LARGE BORE PCI TRIAL

Title:	Ultrasound guided transfemoral complex large bore pci trial
Short title	UltraCOLOR trial
Protocol number and version	V 1.1 March 2nd 2021
Sponsor:	Maatschap Cardiologie Zwolle
Version:	1.0, February 6th 2023
Statistician:	J.J.E. Kolkman

Table of contents

1. Introduction

1.1 Preface

Although the transradial access site is nowadays predominantly used for the vast majority of coronary procedures, transfemoral access is used in a considerable proportion of complex percutaneous coronary intervention (PCI) when large bore guiding catheters are mandated. Especially in case of contra-indication for large bore radial access or the need for dual arterial access (hybrid PCI of chronic total occlusion (CTO)), large bore transfemoral access is frequently used. However, bleeding and vascular complications are strongly associated with femoral access, especially when large bore cannulation is used. The application of ultrasound guidance for large bore femoral access might reduce the occurrence of clinically relevant bleeding and vascular complications.

1.2 Purpose of the analyses

Primary purpose is to investigate if ultrasound guided large bore transfemoral (TF) large bore complex PCI is associated with less access site related bleeding and/or vascular complications as compared with fluoroscopy guided large bore TF complex PCI.

1.3 Scope

This SAP is based on the final protocol version 1.1 March 2nd, 2021. This SAP covers all endpoints for the UltraCOLOR trial. Deviations from the Statistical Analyses Plan will be justified in the study report. Exploratory analyses not necessarily identified in this SAP may be performed to support planned analyses. Any post-hoc or unplanned analyses not specified in this SAP will be identified as such in the statistical report. The work in this study will be performed according to the Standard Operating Procedures of Diagram, in accordance with the principles of GCP and ICHE9.

2. Study objectives and endpoints

2.1 Study Objective

Primary aim of the current study is to demonstrate that ultrasound guided TF access is associated with less access site related bleeding and/or vascular complications as compared with fluoroscopy guided TF access for PCI for complex coronary lesions with large bore ≥ 7 French guiding catheters.

2.2 Endpoints

The primary endpoint is defined as BARC type 2, 3 or 5 bleeding or vascular complication related to the primary femoral access site[12] during hospitalization.

Secondary endpoints are defined as:

- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the primary femoral access site at 30-day follow-up
- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the secondary femoral or radial access site (at discharge and at 30-day follow-up)
- MACE (at discharge and at 30-day follow-up)
- Vascular complication not requiring intervention of the primary femoral access site (at discharge and at 30-day follow-up)
- Vascular complication not requiring intervention of the secondary femoral or radial access site (at discharge and at 30-day follow-up)
- Procedural duration
- Time to access
- First pass puncture
- Number of access attempts
- Accidental venepuncture
-Cross-over
- Suboptimal femoral sheath placement, based on the ileofemoral angiogram

3. Study Methods

3.1 Design of the trial

This study is a prospective, multicenter, randomized, investigator-initiated study designed to enroll 542 patients undergoing PCI for complex coronary lesions through at least one ≥ 7 French transfemoral access who will be randomized 1:1 to either ultrasound or fluoroscopy guided transfemoral access.

A data safety monitoring board (DSMB) will be appointed to assess the safety of the patients in the study. All AEs will be reported to the DSMB and reviewed at planned meetings

throughout the subject enrollment and follow-up period as specified in the DSMB charter to ensure the safety of subjects enrolled in this study.

A clinical endpoint committee will be appointed to centrally adjudicate all safety endpoint clinical study events.

The study duration is approximately 3 years: 36 months enrolment. Follow-up will take place at 30 days post index PCI.

The study was planned to start in June 2021 with an expected duration of patient enrolment of 36 months. The study will be considered finished when all patients have completed the 30 days follow-up.

3.2 Eligibility criteria

Patients are eligible for study participation when PCI is indicated for complex coronary lesions and:

- Use of the femoral artery for primary or secondary access with ≥ 7 Fr guiding catheter as indication for complex PCI, according to the expertise of the treating physician.
- Age 18 years or older.

Exclusion criteria:

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

- Inability to obtain informed consent
- Contra-indication for femoral access
- Cardiogenic shock
- ST elevation myocardial infarction

3.3 Randomisation and blinding

After providing written informed consent eligible subjects are randomly assigned to receive one of the two study treatments, ultrasound guided large bore transfemoral access or

fluoroscopy guided large bore transfemoral access, in a 1:1 ratio. Treatment assignments are performed centrally through a dedicated website as part of the electronic Case Report Form (e-CRF) according to a computer-generated random schedule in random permuted blocks with stratification by site.

4. Sample size

The appropriate sample size was estimated at n= 271 subjects, based on a superiority design with a type 1 error rate of 5% and a power of 80%, assuming a 16% complication rate in the comparator group and 49% reduction (7.84% complication rate) in the ultrasound guided group (14). Therefore a total of 542 subjects (271 subjects in each group) needs to be randomized in this trial. Since the primary endpoint is scored at discharge, there is no need for incorporating a loss-to-follow-up percentage in the sample size calculation.

5. General Considerations

5.1 Timing of analyses

The final analysis of the primary objective will take place after the follow up of last patient in. Data should meet the cleaning and approving requirements and the SAP should be finalised and approved.

The cleaning and approving requirements are:

- All expected CRFs have been entered
- All queries are resolved
- All data are consistent
- Data is determined to be clean
- The expected site signatures have been applied
- Data has been locked

5.2 Definition of analysis sets

This section is designed to identify the characteristics needed for inclusion in particular populations used in the analysis.

5.2.1 Full Analysis Set

- Patients are considered enrolled when they have signed informed consent and after the randomization assignment has been made.
- Patients enrolled in the study with major deviations will also be analyzed in the full analysis set.

5.2.2 Per-Protocol (PP) Analysis Set

All subjects enrolled in the study who signed informed consent, who were treated by the randomized strategy (no cross over to other strategy) with no major protocol deviations, will be included in the Per-Protocol Analysis Set.

Major protocol deviations are defined as:

- Access strategy not according to randomized assignment
- Whose informed consent was not properly obtained
- Not meeting the in- and exclusion criteria
- Different sheath size used (smaller than 7 Fr)

5.2.3 Safety Analysis Set

The safety population will be defined as all randomised subjects who underwent complex PCI, and will be classified according to the actual treatment received.

5.3 Examination of subgroups

Subgroup analyses will be performed including several potential differing treatment effects for the following groups.

- Age < 75 years versus ≥ 75 years,
- Male versus female sex
- Obesity defined as Body Mass Index <30 versus ≥ 30
- Underweight defined as Body Mass Index <18,5 versus ≥ 18,5
- Presence versus absence of hypertension
- Presence versus absence of peripheral arterial disease
- Presence versus absence of severe renal dysfunction (Modification of Diet in Renal Disease (MDRD) <30ml/1.73m2 versus ≥ 30)
- Pre-existent anemia (hemoglobin <6.8 mmol/l versus ≥6.8 mmol/l)

- Pre-existent thrombocytopenia (thrombocytes < 100 x 10^9/L versus ≥ 100 x 10^9/L)
- Final ACT <150 versus ≥ 150 seconds right before sheath removal
- Suboptimal versus optimal sheath placement
- 7-F versus 8-F sheath size
- CTO versus non-CTO PCI
- Acute coronary syndrome versus chronic coronary syndrome presentation
- Vascular closure device use versus no vascular closure device use
- Peri-procedural active oral anticoagulant therapy versus no active or absent oral anticoagulant therapy

Subgroups were not prespecified in the protocol

Subgroup analyses will not be performed for a specific subgroup if the sample size in one or more arms of this subgroup is too low to perform a valid analysis

Subgroup analyses will be performed for interaction with the primary endpoint (BARC 2,3 or 5 bleeding or vascular complication requiring intervention of the primary access site) at discharge as well as 30 day follow-up.

Subgroup analyses will focus on the evidence for a difference in treatment effects: the interaction effect. By the use of forest plot figures the relevant information about possible subgroup effects and interactions will be presented. The interaction test is carried out as part of a logistic regression model. The logistic regression model contains the randomized treatment term, the subgroup classification term (e.g. males versus females) and the treatment x subgroup interaction term. If the p value for the interaction test is statistically significant, the null hypothesis will be rejected and a significant “treatment x subgroup interaction” can be claimed.

5.4 Missing data

We will describe patterns in missing data. The data collected from the patient until the time of study discontinuation will be used in the data analysis. We will analyse whether missing data in follow-up are related to values on baseline values or values on earlier time points.

In case data on all cause mortality, MI or repeat revascularization is missing at 30 days, follow-up is censored at the moment of last contact.

5.5 Interim analysis

No interim analysis is performed.

5.6 Multi-centre trials

Individual centre results will be presented where appropriate, e.g. when the centres have sufficient numbers of subjects to make such an analysis potentially valuable. The possibility of qualitative or quantitative treatment-by-centre interaction should be explored. Sites with 10 subjects or less will be combined for this analysis. Any extreme or opposite result among centres will be noted and discussed, considering such possibilities as differences in study conduct, patient characteristics, or clinical settings. Treatment comparison will include analyses that allow for centre differences with respect to response. If appropriate, demographic, baseline and post-baseline data, as well as efficacy data, will be presented by centre, even though the combined analysis is the primary one.

6. Summary of study data

Descriptive statistics will be provided for all variables considered in the analysis. All continuous variables will be summarised uding the following descriptive statistics: where applicable, N (non-missing sample size), mean, standard deviation (SD), median, interquartile range, minimum (min) and maximum (max). The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, treatment group and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for the overall group and one for each treatment in the order (Ultrasound guided, Fluoroscopy guided) and will be annotated with the total population size relevant to that table/treatment, including any missing observations. Only deviations from the general overview will be noted in the subsections within section 6.2.

6.1 Subject disposition

The number of patients included, completed baseline and 30 days follow up and how many dropped out and for what reasons (death, withdrew consent, etc.) will be presented together

with the number of subjects in each analysis set. Numbers will be presented overall, by treatment group and by centre.

6.2 Protocol deviations

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment should be described.

Protocol deviations will be appropriately summarized by centre, treatment group and are grouped into different categories, such as:

- Those who entered the study even though they did not satisfy the entry criteria
- Those in which the randomisation procedure was not correct applied
- Those in which the informed consent procedure was not correct applied
- Those in which procedure was not as described in protocol
- Those in which the follow up visit schedule was not followed

Major deviations could impact the analysis. Major is defined in section 5.2.2.

6.3 Demographic and baseline variables

Demographic and baseline variables will be summarised by treatment group and overall in the full analysis set and per protocol analysis set.

Demographic variables:

age
sex
Height, cm
Weight, kg
BMI, kg/m2 (calculated)

Medical history/ risk factors prior to index hospitalisation:

Diabetes Mellitus
Active smoking
Hypercholesterolemia
Hypertension
Familiy history of CAD
Previous MI

Previous PCI

Previous CABG

Previous Stroke

Peripheral arterial disease

Indication for complex PCI

Stable angina

ACS

Heart failure

Arrhythmia

Left ventricular ejection fraction, n (%)

Poor (<30%)

Moderate (30-50%)

Good (≥50%)

Laboratory:

MDRD

Hemoglobin

Thrombocytes

Reason for 7-F femoral

Radial artery(ies) too small for 7 Fr access (based on previous experience, palpation or ultrasound)

Radial artery(ies) occluded/not palpable

Combination femoral/radial access for hybrid CTO is standard practice/operators preference

Patients' preference

Previous radial access issues (i.e. spasm, tortuosity)

6.4 Treatment compliance

Treatment compliance will be assessed based on the data, checked by monitor, about procedural access strategy.

7. Efficacy analyses

All efficacy variables will be listed by subject within study centre. Data will be summarised by treatment group.

7.1 Primary Efficacy Analysis

The primary endpoint is the composite endpoint rate, including BARC type 2, 3 or 5 bleeding or vascular complication related to the primary access strategy (during hospitalization). Vascular complication is defined as retroperitoneal hematoma, (pseudo) aneurysm, infection and arteriovenous-fistula or vascular occlusion requiring intervention.

The primary analysis will be carried out on the full analysis population for efficacy. The analysis will be performed according to the intention-to-treat principle (i.e. the subjects are grouped in the treatment they are randomised to, but not necessarily the one they received).

Differences in absolute outcome value (incidences) will be statistically tested between groups by using Pearson's chi-squared test. In case of rare events (the expected number per cell lower than 5 in more than 20% of the cells) the Fisher Exact test will be used.

The two treatment groups will be compared on baseline measurements to investigate whether these are evenly distributed across the two arms. In case the randomised groups differ in important baseline measurements a multiple logistic regression analysis will be performed controlling for the relevant confounders as secondary analysis.

All statistical tests will be interpreted at a 2-sided significance level of 0.05 and all confidence intervals at a 2-sided level of 95% unless otherwise stated.

Additionally, the primary analysis will be tested in the per-protocol analysis set and the results will be used as supportive sensitivity analysis for the efficacy assessments.

7.2 Secondary Efficacy Analysis

For secondary endpoints, differences in absolute outcome values (incidences) will be statistically tested between groups by using Pearson's chi-squared test. In case of rare events

(the expected number per cell lower than 5 in more than 20% of the cells) the Fisher Exact test will be used. Depending on the distribution of the data, T-tests or Mann-Whitney U tests will be used for continuous data.
The time to event for MACE will be plotted by means of Kaplan-Meier survival curves. In case a patient is lost to follow-up or the outcome variable is missing we will use the latest time available if the event of interest did not occur during the observation period (censoring). We will test for differences between the survival distributions in the two treatment groups by means of the logrank test.

All tests are two-sided and an alpha of 5% will be used as the level of significance.

In table 1 the summary statistics and statistical tests for each of the secondary end points are depicted.

Table 1. Summary statistics and statistical test per secondary endpoint

Secondary endpoint	**Summary statistic**	**Statistical test**
BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the secondary femoral or radial access site during index hospitalization.	-number and % in both groups	Chi2 or Fisher exact test
BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the primary femoral access site at 1 month	-number and % in both groups	Chi2 or Fisher exact test
BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the secondary femoral or radial access site at 1 month	-number and % in both groups	Chi2 or Fisher exact test

MACE (hospitalization and 1 month)	-number and % in both groups -Kaplan-Meier survival analysis (30 days)	Chi2 or Fisher exact test Logrank test
Number of access attempts	- median (Q1 – Q3) in both groups	T-test or Mann-Whitney U test
First pass puncture	-number and % in both groups	Chi2 or Fisher exact test
Procedural duration	- median (Q1 – Q3) in both groups	T-test or Mann-Whitney U test
Accidental venipuncture	-number and % in both groups	Chi2 or Fisher exact test
Suboptimal sheath placement height	-number and % in both groups	Chi2 or Fisher exact test
Vascular complication not requiring intervention of the primary femoral access site (hospitalization and 1 month)	-number and % in both groups	Chi2 or Fisher exact test
Vascular complication not requiring intervention of the secondary femoral or radial access site (hospitalization and 1 month)	-number and % in both groups	Chi2 or Fisher exact test

8. Safety analyses

This section specifies the methods of describing the safety data. The safety analysis set will be used to describe the safety. Safety data will be summarized in tables by treatment, centre and overall.

8.1 Adverse events

Any observed or reported adverse event that occurs during the study will be recorded on the AE page of the eCRF.

An overall summary table of AE information will be presented to summarize the frequencies and percentages of patients experiencing one or more of the following: adverse events, treatment related AEs, death, serious adverse event (SAE).

Similar summaries will be presented by severity. If a patient has more than one occurance of and AE, the most severe occurance of and AE will be used in the severity summary table. Additional tables will be provided for those adverse events related to study treatment and SAE.

8.2 Deaths, Serious Adverse Events and other Significant Adverse events

Deaths and serious adverse events will be listed in patient level by treatment group.

8.3 Clinical laboratory evaluations

No study-related laboratory evaluations will be performed for this trial.

9. Amendment on the statistical analysis plan

In case of an amendment of the protocol or for other reasons the statistical analysis plan may be amended accordingly. All amendments will be logged and registered.

10. Conduct of statistical analysis

All statistical calculations will be performed using SAS version 9.4 or higher. Statistical analysis will be performed by an independent statistician from Diagram B.V., the Netherlands.

11. Reporting conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

Supplementary Table 1. Lesion and procedural characteristics.

	Fluoroscopy guided (n=270)	Ultrasound guided (n=274)	p-value
Lesion type			
CTO, n (%)	170 (62)	174 (65)	0.85
J-CTO score, median (IQR)	*2.0 (1-3)*	*2.0 (1-3)*	0.42
J-CTO score n (%)			0.71
0	*6 (3)*	*10 (6)*	
1	*48 (28)*	*44 (25)*	
2	*62 (37)*	*54 (31)*	
3	*30 (18)*	*33 (19)*	
4	*22 (13)*	*28 (16)*	
5	*2 (1)*	*5 (3)*	
Final CTO wiring			0.50
AWE	*113 (66)*	*125 (72)*	
ADR	*22 (13)*	*14 (8)*	
RWE	*16 (10)*	*16 (9)*	
RDR	*19 (11)*	*19 (11)*	
Left main, n (%)	28 (10)	30 (11)	0.89
Unprotected	*22 (82)*	*22 (73)*	0.64
Distal	*21 (74)*	*25 (83)*	0.43
Heavy calcification, n (%)	29 (11)	31 (11)	0.90
Rotational atherectomy used	*10 (34)*	*15 (48)*	
Orbital atherectomy used	*1 (3)*	*2 (6)*	
Intravascular lithotripsy used	*8 (28)*	*5 (16)*	
Complex bifurcation, n (%)	26 (9)	27 (10)	0.99
Medina class, n (%)			0.14
1,1,1	*13 (50)*	*11 (46)*	
1,0,1	*0*	*3 (11)*	
0,1,1	*3 (12)*	*5 (19)*	
Other/unknown	*10 (38)*	*8 (24)*	
Number of vessels diseased , n (%)			0.91
1	109 (41)	114 (42)	
2	80 (30)	78 (28)	
3	66 (24)	71 (26)	
Unknown	15 (5)	11 (4)	
Total stent length (mm)	61 (44-89)	70 (38-96)	0.18

ADR-antegrade dissection and re-entry, AWE-antegrade wire escalation, CTO-chronic total occlusion, ECLS-extracorporeal life support, IABP-intra-aortic balloon pump, IQR-interquartile range, J-CTO score-Japan chronic total occlusion score, mm-millimetres, RWE-retrograde wire escalation, RDR-retrograde dissection and re-entry

Supplementary Table 2. Antiplatelet and anticoagulant therapy.

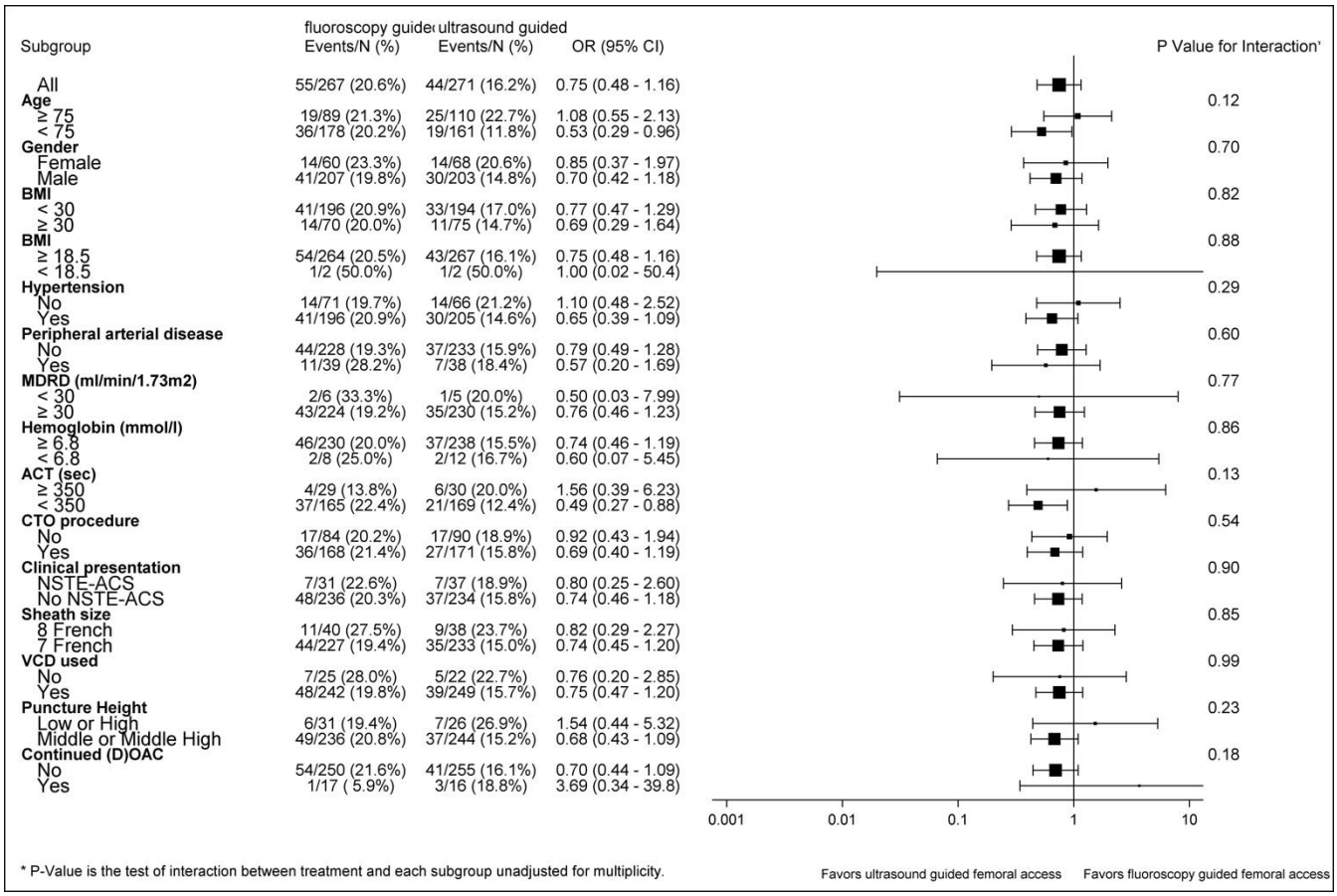
	Fluoroscopy guided (n=270)	Ultrasound guided (n=274)	p-value
Admission			
ASA, n (%)	224 (83)	233 (85)	0.51
P2Y12 inhibitor, n (%)	210 (78)	206 (75)	0.48
Clopidogrel	*178 (85)*	*162 (79)*	
Prasugrel	*6 (3)*	*6 (3)*	
Ticagrelor	*26 (12)*	*38 (18)*	
DOAC, n (%)	44 (16)	44 (16)	0.94
Stopped before procedure	*27 (61)*	*28 (64)*	*0.83*
Coumarin, n (%)	7 (3)	9 (3)	0.80
Stopped before procedure	*5 (71)*	*7 (75)*	*0.77*
LMWH, n (%)	0	2 (1)	0.50
Fondaparinux, n (%)	0	1 (<1)	1.0
Per procedure			
Total heparin (iu), median (Q1-Q3)	10000 (7500-12500)	10000 (8000-12500)	0.56
ACT before sheath removal (s), median (Q1-Q3)	251 (211-299)	251 (214-310)	
GP2B/3A inhibitors, n (%)	1 (<1)	1 (<1)	1.0

ACT-activated clotting time, ASA- acetylsalicic acid, DOAC- direct anticoagulant therapy, IQR-interquartile range, LMWH-low molecular weight heparin

Supplementary Table 3. Hospital stay and access site imaging.

	Fluoroscopy guided (n=270)	Ultrasound guided (n=274)	p-value
Hospital stay in days, median (IQR)	1.0 (1-1)	1.0 (1-1)	0.91
Delayed discharge, n (%)	56 (21)	59 (21.5)	0.82
Due to access site complications	*22 (39)*	*26 (44)*	
Due to other complications	*25 (45)*	*18 (31)*	
Due to logistical reasons/other	*9 (16)*	*15 (25)*	
Delay in hours, median (IQR)	24 (5-48)	24 (8-96)	
Imaging access site performed			
Ultrasound, n (%)	24 (9)	18 (7)	0.31
Superficial hematoma	*8 (34)*	*2 (11)*	
Retroperitoneal hematoma	*2 (8)*	*0*	
Arteriovenous shunt	*0*	*0*	
False aneurysm	*2 (8)*	*1 (6)*	
Other complication	*1 (4)*	*4 (22)*	
No complication	*11 (46)*	*11 (61)*	
Computed tomography, n (%)	5 (2)	6 (2)	0.78
Superficial hematoma	*1 (20)*	*3 (50)*	
Retroperitoneal hematoma	*3 (60)*	*3 (50)*	
Arteriovenous shunt	*0*	*0*	
False aneurysm	*0*	*0*	
Other complication	*0*	*0*	
No complication	*1 (20)*	*0*	

IQR-interquartile range



Supplementary Figure 1. Subgroup analysis at 30-day follow-up.
ACT-activated clotting time, BMI-body mass index, CI-confidence interval, CTO-chronic total occlusion, (D)OAC-(direct) oral anticoagulants, NSTE-ACS-Non ST elevation acute coronary syndrome, MDRD- Modification of Diet in Renal Disease