

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Complex Large-Bore Radial Percutaneous Coronary Intervention: Design and Rationale of the COLOR trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038042
Article Type:	Protocol
Date Submitted by the Author:	25-Feb-2020
Complete List of Authors:	Meijers, Thomas; Isala Hospitals, Cardiology Aminian, Adel ; Centre Hospitalier Universitaire de Charleroi, Cardiology Teeuwen, Koen; Catharina Hospital, Cardiology van Wely, Marleen; Radboudumc, Cardiology Schmitz, Thomas; Elisabeth-Krankenhaus-Essen GmbH, Cardiology Dirksen, Maurits; Noordwest Ziekenhuisgroep, Cardiology van der Schaaf, Rene; OLVG, Cardiology Iglesias, Juan; Geneva University Hospitals, Cardiology Agostoni, Pierfrancesco; ZNA, Cardiology Dens, Joseph; Ziekenhuis Oost-Limburg, Cardiology Knaapen, Paul; Amsterdam UMC - Locatie VUMC, Cardiology Rathore, Sudhir; Frimley Health NHS Foundation Trust, Cardiology Ottervanger, Jan Paul; Isala Hospitals, Cardiology Dambrink, Jan-Henk; Isala Hospitals, Cardiology Roolvink, Vincent; Isala Hospitals, Cardiology Gosselink, Marcel; Isala Hospitals, Cardiology Hermanides, Renicus; Isala Hospitals, Cardiology van Royen, Niels; Radboudumc, Cardiology van Leeuwen, Maarten; Isala Hospitals, Cardiology
Keywords:	Coronary intervention < CARDIOLOGY, CARDIOLOGY, Coronary heart disease < CARDIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Complex Large-Bore Radial Percutaneous Coronary Intervention: Design and Rationale of the COLOR trial

Thomas A. Meijers MD^{a*}, Adel Aminian MD^{b*}, Koen Teeuwen MD, PhD^c, Marleen van Wely MD^d, Thomas Schmitz MD, PhD^e, Maurits T. Dirksen MD, PhD^f, René J. van der Schaaf MD, PhD^g, Juan F. Iglesias MD, PhD^h, Pierfrancesco Agostoni MD, PhDⁱ, Joseph Dens MD, PhD^j, Paul Knaapen MD, PhD^k, Sudhir Rathore MD, FRCP^l, Jan Paul Ottervanger MD, PhD^a, Jan Henk E. Dambrink MD, PhD^a, Vincent Roolvink MD, PhD^a, A.T. Marcel Gosselink MD, PhD^a, Recinus S. Hermanides MD, PhD^a, Niels van Royen MD, PhD^d, Maarten A.H. van Leeuwen MD, PhD^a

* Both authors contributed equally.

Word count: 2672

Departments and institutions

^a Department of Cardiology, Isala Heart Center, Zwolle, the Netherlands

^b Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium

^c Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands

^d Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands

^e Department of Cardiology, Elisabeth Krankenhaus, Essen, Germany

^f Department of Cardiology, Northwest Clinics, Alkmaar, the Netherlands

^g Department of Cardiology, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the Netherlands

^h Department of Cardiology, Geneva University Hospital, Geneva, Switzerland

ⁱ Department of Cardiology, ZNA Middelheim, Antwerp, the Netherlands

^j Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium

^k Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands

^l Department of Cardiology, Frimley Health NHS Foundation Trust, Surrey, United Kingdom

Sources of funding

Terumo EMEA (Leuven, Belgium) supported this investigator-initiated study by an unrestricted grant.

Conflict of interest

Maarten A.H. van Leeuwen, Adel Aminian and Juan F. Iglesias are consultants for Terumo corp., Juan F. Iglesias and Thomas Schmitz have received honoraria/speakers fee for Terumo corp., the other authors have no conflicts of interest to declare.

Clinical trial registration

ClinicalTrials.gov identifier: NCT03846752.

Address for correspondence

dr. M.A.H. van Leeuwen, Isala Heart Center, Dr. van Heesweg 2, 8025 AB Zwolle, The Netherlands. Email: m.a.h.van.leeuwen@isala.nl

Abstract

Introduction

The radial artery has become the standard access site for percutaneous coronary intervention (PCI) in stable coronary artery disease and acute coronary syndrome, because of less access site related bleeding complications. Patients with complex coronary lesions are underrepresented in randomized trials comparing radial with femoral access with regard to safety and efficacy. The femoral artery is currently the most applied access site in patients with complex coronary lesions, especially when large bore guiding catheters are required. With slender technology, transradial PCI may be increasingly applied in patients with complex coronary lesions when large bore guiding catheters are mandatory and might be a safer alternative as compared to the transfemoral approach.

Methods and analysis

A total of 388 patients undergoing complex PCI will be randomized to radial 7 French access with Terumo Glidesheath Slender (Terumo Corp., Japan) or femoral 7 French access as comparator. The primary outcome is the incidence of the composite end-point of clinically relevant access site related bleeding and/or vascular complications requiring intervention. Procedural success and major adverse cardiovascular events up to 1 month will also be compared between both groups.

Ethics and dissemination

Ethical approval for the study was granted by the local Ethics Committee at each recruiting center. The trial outcomes will be published in peer-reviewed journals of the concerned literature. The COLOR trial has been administered in the ClinicalTrials.gov database, reference number: NCT03846752.

Strengths and limitations of this study

- First randomized controlled trial comparing radial and femoral access for large bore complex PCI
- Patient enrollment at high-volume centers by operators with ample experience in complex PCI both through femoral and radial access
- Clinical Event Committee adjudicated primary endpoint
- First study assessing extremity dysfunction after complex large bore PCI
- May change daily clinical practice.

Keywords

Complex percutaneous coronary intervention - Chronic total occlusion - Radial access - Femoral access - Slender

Abbreviations

PCI = percutaneous coronary intervention

CTO = chronic total occlusion

CABG = coronary artery bypass grafting

ACS = acute coronary syndrome

BARC = bleeding academic research consortium

MACE = major adverse cardiovascular events

AE = adverse event

SAE = serious adverse event

TR= transradial

TRA= transradial access

1
2
3 TF = transfemoral
4 TFA = transfemoral access
5 Fr = French
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Background

The radial artery has become the standard access site for percutaneous coronary interventions (PCI), driven not only by lower rates of major bleeding and vascular complications, but also by reduced mortality in patients presenting with acute coronary syndrome (ACS) (1–3). This has led the 2018 ESC/EACTS Guidelines on myocardial revascularization to recommend transradial access (TRA) over transfemoral access (TFA) as a class Ia indication in ACS patients undergoing invasive management (4). In patients with stable coronary artery disease, several small randomized trials comparing radial and femoral access have shown significantly less bleeding in favor of radial access but no mortality benefit (5–7). Of note, patients with complex coronary lesions were not included in these trials or not specifically described. PCI of chronic total occlusions (CTO), left main disease, heavily calcified or complex bifurcation lesions often require the use of large-bore guiding catheters (7 Fr or larger inner diameter). Indeed, large-bore guiding catheters provide more back-up and stability in addition to better materials' compatibility, leading to higher procedural success rates in more complex lesions (8,9). Because of potential radial artery-sheath mismatch, spasms or back-up problems, the femoral artery is still the most applied access site for complex PCI (10,11). In return, TFA with increased sheath size is associated with bleeding and vascular complications and adverse clinical outcome, including myocardial infarction (MI), stroke and death (12,13). The recent availability of modern slender technology, such as the thin-walled radial introducer sheath (Glidesheath Slender®, Terumo Corp., Japan), has the potential to expand the use of TRA for complex PCI. As compared to the average outer diameter of a standard sheath, the outer diameter of these slender sheaths has been reduced by approximately 1 Fr while maintaining the inner-diameter equivalent. In a prospective single-arm study it was recently shown that complex TR PCI with a 7 Fr Glidesheath Slender is safe and effective (14). Several observational studies have been published describing feasibility of large bore TRA for PCI of CTO's, left main disease, heavily calcified lesions and complex bifurcations without affecting procedural success rates (9,11,15–18). However, randomized data comparing TRA and TFA for percutaneous treatment of complex coronary lesions are lacking. Therefore, we have designed a randomized study, comparing the safety and efficacy of TRA and TFA for complex PCI using large-bore guiding catheters.

Methods

Study design

The Complex Large-Bore Radial PCI (COLOR) trial is an investigator-initiated international multi-center study with a prospective, randomized controlled design. Participating centers are the Isala Heart Center (Zwolle, the Netherlands), Catharina Hospital (Eindhoven, the Netherlands), Radboud University Medical Center (Nijmegen, The Netherlands), Elisabeth-Krankenhaus (Essen, Germany), NorthWest Clinics (Alkmaar, the Netherlands), Onze Lieve Vrouwe Gasthuis Hospital (Amsterdam, the Netherlands), Centre Hospitalier Universitaire de Charleroi (Charleroi, Belgium), ZNA Middelheim (Antwerpen, Belgium), Hospital Oost-Limburg (Genk, Belgium), VU University Medical Center (Amsterdam, The Netherlands) and Frimley NHS (Surrey, United Kingdom).

Trial organization

The trial is approved by the appropriate ethics review board at each clinical site. Written informed consent will be obtained from all patients before enrollment. The trial was designed in accordance with the declaration of Helsinki. All data will be collected in an electronic data capturing system, the eDREAM (electronic case record form Diagnostic REsearch And Management). Diagram BV, Zwolle, the Netherlands will be responsible for overall trial and data management, as well as monitoring of the study. Evaluation of serious adverse events is

1
2
3 being performed by an independent Data Safety Monitoring Board (DSMB). A Clinical
4 Events Committee (CEC) will review and adjudicate all end-point related adverse events. The
5 COLOR trial has been administered in the ClinicalTrials.gov database, reference number:
6 NCT03846752.
7

8 9 *Objectives*

10 The primary objective of this study is to investigate whether TR PCI is superior to TF PCI in
11 complex coronary lesions with large-bore guiding catheters with respect to clinically relevant
12 access site related bleeding and/or vascular complications.
13

14 As secondary objectives, TR and TF large-bore access will be compared with regard to
15 procedural success, procedural time, fluoroscopy time, contrast use, crossover rates, major
16 adverse cardiovascular events (MACE) and non-access site related bleeding or vascular
17 complications for complex PCI.
18

19 For exploratory purposes extremity dysfunction and discomfort will be compared between TR
20 and TF treated patients for complex PCI with large-bore guiding catheters.
21
22

23 24 *Inclusion (figure 1)*

25 All patients of 18 years or older, presenting with stable coronary artery disease, unstable
26 angina or non-ST elevation myocardial infarction and planned for complex PCI of CTO
27 (defined as lesion exhibiting TIMI 0-1 flow in a native coronary artery with an occlusion
28 duration of ≥ 3 months), left main, complex bifurcation or heavy calcification, in whom the
29 operator anticipates that a 7 Fr guiding catheter is indicated, are screened for inclusion.
30 Patients with ST elevation myocardial infarction or cardiogenic shock will be excluded.
31 Patients with contraindications for femoral or radial access, such as occlusive peripheral
32 artery disease, known severe spasm or known anatomical variants prohibiting radial or
33 femoral access on both sides will be excluded as well.
34
35

36 37 *Randomization*

38 After providing written informed consent, eligible subjects are randomly assigned to receive
39 one of the two study treatments in a 1:1 ratio. Treatment assignments are performed centrally
40 through a dedicated website as part of the electronic Case Report Form (eCRF) according to a
41 computer-generated random schedule in random permuted blocks with stratification by site
42 (19). There will be no blinding of the randomization assignment.
43
44

45 46 *Endpoints*

47 Clinically relevant access site related bleeding or vascular complication requiring intervention
48 of the randomized access site during hospitalization is defined as primary endpoint. Bleeding
49 will be classified according to the Bleeding Academic Research Consortium (BARC) criteria
50 (20), and considered clinically relevant when the score is ≥ 2 (CEC adjudicated)(21). Severity
51 and type of intervention of vascular complications is specified in the CEC manual (Appendix
52 I).

53 Secondary safety and efficacy endpoints are:

- 54 - Procedural success (defined as angiographic success without in-hospital MACE), procedural
55 time, fluoroscopy time, contrast use and crossover rate (crossover is defined as conversion
56 from TF to TR or vice versa; conversion to contralateral TR or TF access site is not
57 considered crossover).
- 58 - Clinically relevant BARC bleedings or vascular complications (requiring intervention) that
59 are not related to the randomized access (CEC adjudicated)
60

1
2
3 - MACE, defined as composite of death, MI and repeat revascularization, during
4 hospitalization and at 1 month (CEC adjudicated)
5

6 *Index percutaneous coronary intervention and hospitalization*

7 Radial access will be performed according to the local protocol, using direct needle technique
8 or venous cannula technique, followed by introduction of a 7 Fr Glidesheath Slender. A
9 standard cocktail of nitroglycerine and verapamil will be given intra-arterially after radial
10 sheath placement. Femoral access will be performed using direct needle technique, followed
11 by introduction of a standard 7 Fr femoral sheath. Use of ultrasound for vascular access will
12 be left to the operator's discretion. A bolus of unfractionated heparin will be given after
13 sheath placement, adapted to the patient's body weight. Activated clotting time (ACT)
14 measurements will be performed during the procedure according to local protocol. Additional
15 arterial access will be left to the discretion of the operator, i.e. in case of double arterial access
16 for hybrid CTO treatment. PCI will be performed according to standard procedures with
17 modern drug eluting stents. The applied technique for complex PCI will be left to the
18 discretion of the operator. Patent hemostasis after radial access with the reverse Barbeau test
19 is highly recommended (22). The type of femoral artery hemostasis will be left to the
20 discretion of the treating interventional cardiologist; however the application of a closure
21 device is advocated. The visual analogue scale (VAS) will be used to assess post-procedural
22 pain of the access site(s). Before discharge the access site(s) will be checked for bleeding and
23 vascular complications. Radial artery patency will be checked with the reverse Barbeau test
24 (22). Additional ultrasound or doppler will be performed in those patients with suspected
25 radial or femoral occlusion or the presence of other vascular complications.
26
27
28
29

30 *Extremity dysfunction*

31 Two validated questionnaires will be used to assess the occurrence of upper and lower
32 extremity dysfunction. Upper extremity function will be measured with the QuickDASH
33 (Quick Disabilities of Arm, Shoulder and Hand) score (23) measured at baseline (before PCI)
34 and at 1 month follow-up. Lower extremity function will be measured with the LEFS (Lower
35 Extremity Functional Scale) (24). Both questionnaires are valid, reliable and responsive to
36 monitor and assess pain and function of the extremities.
37
38
39

40 *Follow-up*

41 Follow-up will be performed 1 month after index procedure discharge by either phone call or
42 outpatient clinic visit. MACE and access site bleeding or vascular complications will be
43 documented. Extremity function and discomfort will be assessed, using the aforementioned
44 scores. Adverse Events (AE's) will be monitored from inclusion to one-month follow-up and
45 will be assessed by an independent DSMB, composed of two experienced cardiologists and
46 one statistician, reviewing patient safety and study integrity.
47
48

49 *Sample size calculation and statistics*

50 Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the
51 proportion of access site related bleeding or vascular complication to be 3.5% with radial
52 access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1)
53 will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients
54 will be needed. Data will be analyzed according to the intention-to-treat analysis. All
55 statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically
56 significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago,
57 Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-
58 Square test will also be used for our secondary objectives with binary outcomes. For our
59
60

1
2
3 secondary objectives with continuous variables we will use the Student's t-test (normally
4 distributed) or the Mann-Whitney U test (non-normally distributed). Statistical analysis will
5 be performed by an independent contract research organization (Diagram BV, Zwolle, the
6 Netherlands).
7

8 *Patient and Public Involvement*

9 No patients were involved in the development of the research question or design of this study.
10
11

12 *Ethics and dissemination*

13 Ethical approval for the study was granted by the local Ethics Committee at each recruiting
14 center. The trial outcomes will be published in peer-reviewed journals of the concerned
15 literature.
16
17

18 **Discussion**

19 TRA is nowadays the standard for PCI, mainly driven by the lower risk of bleeding and
20 vascular complications compared to TFA, with even a mortality benefit in ACS patients
21 (2,3,25,26). Randomized data in patients with stable coronary artery disease are limited and
22 more heterogeneous, and show less beneficial effect of radial over femoral access (1,27,28).
23 Moreover, complex coronary lesions are absent or at least not specifically described in most
24 trials supporting current guidelines on myocardial revascularization. Currently, the femoral
25 artery is still considered the preferred access site for complex PCI by many operators
26 (11,16,29–31), despite the increased risk of bleeding and vascular complications, especially
27 when large bore guiding catheters (≥ 7 Fr) are required (11,32–34). During CTO-PCI, the use
28 of large-bore guiding catheters has been reported in 60-70% of cases and is associated with a
29 higher procedural success rate (9,16). Large-bore guiding catheters have better materials'
30 compatibility, especially when using guide extensions and microcatheters. The use of
31 CrossBoss/Stingray (Boston Scientific, Marlborough, MA, USA) for antegrade dissection/re-
32 entry technique is only possible with large-bore guiding catheters (35). When performing PCI
33 of heavily calcified lesions with rotational atherectomy using large burr sizes, large-bore
34 guiding catheters will be needed as well (36). Application of large-bore guiding catheters for
35 complex PCI of left main and true bifurcations is advocated by experts, though efficacy and
36 safety data are lacking. Limited data show comparable feasibility of TRA versus TFA for left
37 main as well as bifurcation PCI with a tendency towards less bleeding complications(11,37).
38
39
40
41
42

43 The most important argument to refrain from TR PCI for complex coronary lesions is the
44 limited diameter of the radial artery. Current standard 7 Fr radial sheaths have an outer
45 diameter of 2.97-3.19 mm (38). As such, the percentage of patients with a radial artery
46 smaller than the outer diameter of a 7 Fr sheath ranges between 29% and 67% in men and
47 between 60% up to 85% in women (39). This suggests that using a standard 7 Fr sheath for
48 TRA will result in sheath to artery mismatch in a significant proportion of patients, increasing
49 the risk of vascular complications. Radial artery occlusion (RAO) is the most frequent
50 complication after radial access, with increasing RAO rates with increasing sheath size (40).
51 In most instances, RAO will not lead to any clinical sequelae, however in rare cases RAO
52 may require intervention because of extremity dysfunction or ischemia (41,42). Moreover,
53 RAO prohibits future re-cannulation of the radial artery, harvesting the radial artery as
54 conduit for CABG or creating a hemodialysis shunt (43). Other arguments to use the femoral
55 artery for complex PCI have been suggested, such as improved back-up with potential higher
56 procedural success rates and shorter procedural time and lower radiation dose. However, this
57
58
59
60

1
2
3 is not supported by observational data showing similar effectiveness, procedural success rates,
4 cross-over rates, radiation dose and contrast use for TRA and TFA (11,16,17,39).
5

6
7 Several technologies have been developed to facilitate large bore access through the radial
8 artery (44). A sheathless approach for example was shown to be a feasible alternative for
9 large bore radial access (45). The 7.5 Fr Eaucath sheathless guiding catheter (ASAHI Intecc,
10 Aichi, Japan) has the same inner diameter as a regular 7 Fr guiding catheter, but an outer
11 diameter of 2.49 mm, resulting in a large reduction in outer diameter (approximately 2 Fr)
12 compared with a standard 7 Fr sheath (46). However, PCI with sheathless guiding catheters
13 requires specific experience due to the highly hydrophilic coating, and limited evidence exists
14 regarding the true impact on RAO (47,48). Miniaturization of TR equipment can also be
15 achieved through a sheath-based approach. Thanks to a reduction in sheath wall thickness
16 (“slender technology”), thin-walled sheaths have reduced their outer diameter while
17 maintaining the same inner diameter. The 7 Fr Glidesheath Slender (Terumo, Japan) is the
18 first commercially available 7 Fr thin-walled sheath, combining an inner diameter of 2.46mm,
19 compatible with any 7 Fr guiding catheter, with a reduced outer diameter of 2.79mm. A recent
20 prospective multicenter study has shown the feasibility and safety of using the 7 Fr
21 Glidesheath Slender for complex TR-PCI in daily practice with a high rate of procedural
22 success and low rate of vascular complications (14).
23
24
25

26
27 In the literature, several outcome measures have been used to evaluate access site related
28 bleeding complications, such as the Thrombolysis in Myocardial Infarction (TIMI)(49), the
29 Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary
30 arteries (GUSTO)(50) or BARC (20). Access site hematoma size has also been used as an
31 outcome measure in studies comparing radial with femoral access. BARC bleeding ≥ 2 has
32 shown to independently predict 1-year mortality and capture more clinically significant
33 bleeding than TIMI minor/major and GUSTO moderate/severe criteria (20,21). Importantly,
34 hematoma size alone, not meeting criteria for other bleeding outcome measures, has not
35 shown any association with clinically relevant endpoints (51). The current trial will use the
36 BARC bleeding score for the primary outcome measure to detect a clinically relevant
37 difference in bleedings between TRA and TFA for complex PCI, adjudicated by a CEC.
38 Besides bleeding and vascular complications, vascular access may also have a potential effect
39 on extremity function (52,53). Although upper extremity dysfunction is present in a small
40 proportion of patients after TRA, it can lead to important morbidity for the affected patients
41 (52–55). Extremity dysfunction may be more pronounced in patients with large-bore access.
42 In addition, current literature does not provide an insight around prevalence and significance
43 of lower extremity function after TFA (53). Therefore, we will assess the occurrence of
44 extremity dysfunction utilizing the QuickDASH and LEFS questionnaires, which will be
45 valuable information for both patients and doctors.
46
47
48

49
50 In conclusion, The COLOR trial is the first prospective multicenter randomized trial
51 comparing TRA with TFA using large-bore guiding catheters for complex PCI. Currently 290
52 patients are randomized. The results of this trial will provide important insights about the
53 safety and efficacy of large-bore TRA and TFA for complex PCI, with a potential impact on
54 daily practice.
55
56
57
58
59
60

Appendix I

CEC manual for adjudicating bleeding and vascular complications

Classification and Definition

Bleeding

BARC 0

No bleeding or hematoma.

BARC 1

Every bleeding or hematoma not meeting the criteria for BARC 2 or higher.

BARC 2

Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, (prolonged) hospitalization, or treatment by a health care professional. Specified for radial access and femoral access in this appendix

BARC 3a

Overt bleeding + Hb drop of 3-5 g/dl (1.9 – 3.1 mmol/L), or any transfusion with overt bleeding (independent of Hb)

BARC 3b

Overt bleeding + Hb drop >5g/dl (>3.1 mmol/L), or cardiac tamponade, or bleeding requiring surgical intervention and/or IV vasoactive agents

BARC 3c

Intracranial hemorrhage or intraocular bleedings

BARC 4

CABG related bleeding

BARC 5

Fatal bleeding

Vascular complications

Retroperitoneal hematoma, (pseudo) aneurysm, infection and arteriovenous-fistula or vascular occlusion requiring intervention. Specified for radial access and femoral access in this appendix

Radial access

Specification of BARC 2 bleedings

1. Prolonged hospitalization

Any bleeding that leads to one or more extra hospitalization day(s)

- Based on standard discharge policy of hospital

- For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

2. Additional compression therapy

Any additional compression therapy after successful primary hemostasis

- Bleeding after removal of first TR band and additional compression bandage or TR band is needed

Ongoing bleeding with first TR band and additional compression therapy is needed

- Adding 1 or 2cc of air in the first TR band due to slight oozing should not be scored as BARC 2

3. Additional investigations

Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

4. Additional therapy

Any additional or change of therapy related to bleeding/hematoma

- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation of medical therapy (i.e. vitamin K, hematological products)
- Percutaneous intervention (i.e. coiling)

Specification of vascular complications

Vascular complications requiring intervention: percutaneous, surgical, medical

- (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
- Infection (i.e. antibiotics)
- Arteriovenous-fistula (i.e. percutaneous or surgical intervention)
- Radial artery occlusion (percutaneous intervention, heparin therapy)
- Dissection (i.e. percutaneous or surgical intervention)
- Compartment syndrome (i.e. percutaneous or surgical intervention)

Femoral access

Specification BARC 2 bleeding

1. Prolonged hospitalization

Any bleeding that leads to one or more extra hospitalization day(s)

- Based on standard discharge policy of hospital
- For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

2. Additional compression therapy

Any additional compression therapy after successful primary hemostasis:

- New compression therapy after removal of the first bandage, or additional compression after closure device
- Prolonging compression bandage due to slight oozing should not be scored BARC 2, when this will not lead to prolonged hospitalization (one or more days).

3. Additional investigations

Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, angiography or CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

4. Additional therapy

Any additional or change of therapy related to bleeding/hematoma

- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation medical therapy (i.e. vitamin K, hematological products)
- Percutaneous intervention (i.e. coiling or stenting of peripheral arteries)

Specification of vascular complications

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)

References

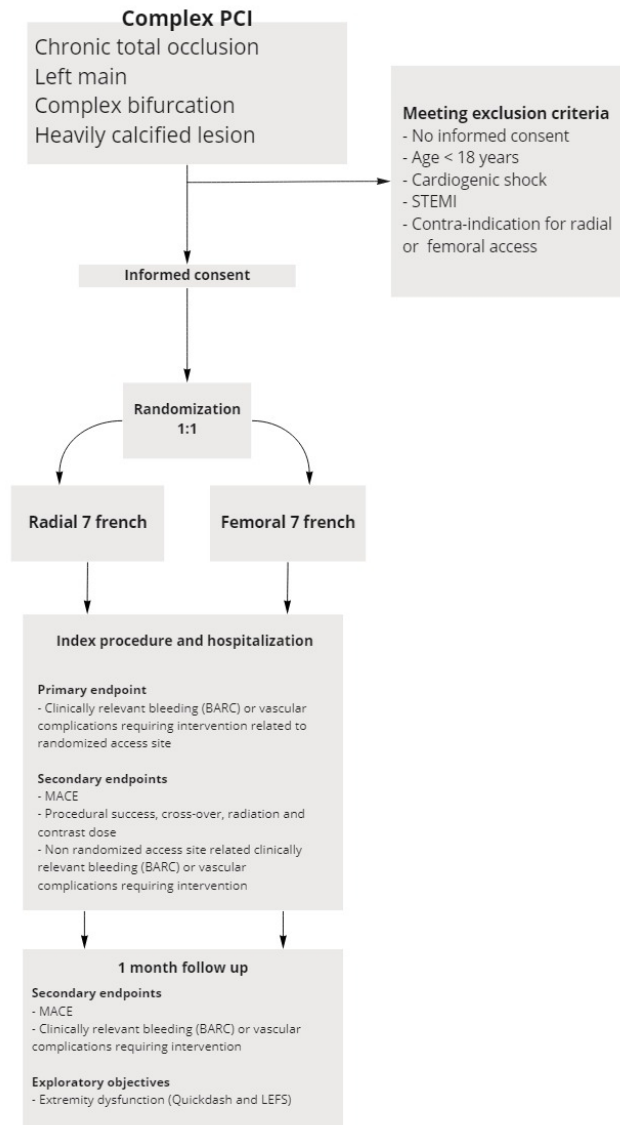
1. Ferrante G, Rao S V., Jüni P, Da Costa BR, Reimers B, Condorelli G, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2016;
2. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet.* 2011;
3. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet.* 2018;
4. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg.* 2019;
5. Ferrante G, Rao S V., Jüni P, Da Costa BR, Reimers B, Condorelli G, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2016;9(14):1419–34.
6. Santas E, Bodí V, Sanchis J, Núñez J, Mainar L, Miñana G, et al. The Left Radial Approach in Daily Practice. A Randomized Study Comparing Femoral and Right and Left Radial Approaches. *Rev Española Cardiol (English Ed.)* 2009;
7. Louvard Y, Benamer H, Garot P, Hildick-Smith D, Loubeyre C, Rigattieri S, et al. Comparison of transradial and transfemoral approaches for coronary angiography and angioplasty in octogenarians (the OCTOPLUS study). *Am J Cardiol.* 2004;
8. Burzotta F, De Vita M, Lefevre T, Tommasino A, Louvard Y, Trani C. Radial approach for percutaneous coronary interventions on chronic total occlusions: Technical issues and data review. *Catheterization and Cardiovascular Interventions.* 2014.
9. Tanaka Y, Moriyama N, Ochiai T, Takada T, Tobita K, Shishido K, et al. Transradial Coronary Interventions for Complex Chronic Total Occlusions. *JACC Cardiovasc Interv.* 2017;
10. Galassi AR, Tomasello SD, Reifart N, Werner GS, Sianos G, Bonnier H, et al. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: Insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. *EuroIntervention.* 2011;
11. Chung S, Her SH, Song PS, Song Y Bin, Hahn JY, Choi JH, et al. Trans-radial versus trans-femoral intervention for the treatment of coronary bifurcations: Results from coronary bifurcation stenting registry. *J Korean Med Sci.* 2013;
12. Smilowitz NR, Kirtane AJ, Guiry M, Gray WA, Dolcimascolo P, Querijero M, et al. Practices and complications of vascular closure devices and manual compression in patients undergoing elective transfemoral coronary procedures. In: *American Journal of Cardiology.* 2012.
13. Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following

- percutaneous coronary interventions. *Am J Cardiol.* 2003;
14. Aminian A, Iglesias JF, Van Mieghem C, Zuffi A, Ferrara A, Manih R, et al. First prospective multicenter experience with the 7 French Glidesheath slender for complex transradial coronary interventions. *Catheter Cardiovasc Interv.* 2017;
 15. Megaly M, Karatasakis A, Abraham B, Jensen J, Saad M, Omer M, et al. Radial Versus Femoral Access in Chronic Total Occlusion Percutaneous Coronary Intervention. *Circ Cardiovasc Interv.* 2019;
 16. Jan Bakker E, Maeremans J, Zivelonghi C, Faurie B, Avran A, Walsh S, et al. Fully transradial versus transfemoral approach for percutaneous intervention of coronary chronic total occlusions applying the hybrid algorithm insights from recharge registry. *Circ Cardiovasc Interv.* 2017;
 17. De Maria GL, Burzotta F, Trani C, Kassimis G, Pirozzolo G, Patel N, et al. Trends and Outcomes of Radial Approach in Left-Main Bifurcation Percutaneous Coronary Intervention in the Drug-Eluting Stent Era: A Two-Center Registry. *J Invasive Cardiol.* 2015;
 18. Rathore S, Hakeem A, Pauriah M, Roberts E, Beaumont A, Morris JL. A comparison of the transradial and the transfemoral approach in chronic total occlusion percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2009;
 19. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. *Control Clin Trials.* 1988;
 20. Mehran R, Rao S V., Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. *Circulation.* 2011;
 21. Vranckx P, White HD, Huang Z, Mahaffey KW, Armstrong PW, Van De Werf F, et al. Validation of BARC Bleeding Criteria in Patients with Acute Coronary Syndromes the TRACER Trial. *J Am Coll Cardiol.* 2016;
 22. Wilson SJ, Mitchell A, Gray TJM, Loh HJ, Cruden NL. Patent haemostasis prevents radial artery occlusion in patients with an acute coronary syndrome. *Int J Cardiol.* 2017;
 23. Beaton DE, Wright JG, Katz JN, Amadio P, Bombardier C, Cole D, et al. Development of the QuickDASH: COMparison of three item-reduction approaches. *J Bone Jt Surg - Ser A.* 2005;
 24. Binkley J, Stratford P, Lott S, Riddle D. The lower extremity functional scale. *Phys Ther.* 1999;
 25. Bernat I, Horak D, Stasek J, Mates M, Pesek J, Ostadal P, et al. ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: The STEMI-RADIAL trial. *J Am Coll Cardiol.* 2014;
 26. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, et al. Radial versus femoral randomized investigation in st-segment elevation acute coronary syndrome: The rifle-steacs (radial versus femoral randomized investigation in st-elevation acute coronary syndrome) study. *J Am Coll Cardiol.* 2012;
 27. Diehl D, de Ribamar Costa J, Costa R, de Mello BG, Chamié D, Jatene T, et al. PROPENSITY-SCORE COMPARISON OF PATIENTS WITH STABLE CORONARY ARTERY DISEASE UNDERGOING PERCUTANEOUS CORONARY INTERVENTION BY RADIAL VERSUS FEMORAL APPROACH. *J Am Coll Cardiol.* 2016;
 28. Rao S V., Hess CN, Barham B, Aberle LH, Anstrom KJ, Patel TB, et al. A registry-based randomized trial comparing radial and femoral approaches in women undergoing percutaneous coronary intervention: The SAFE-PCI for women (study of access site for enhancement of PCI for women) trial. *JACC Cardiovasc Interv.* 2014;

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
29. Koifman E, Gaglia MA, Escarcega RO, Bernardo NL, Lager RA, Gallino RA, et al. Comparison of transradial and transfemoral access in patients undergoing percutaneous coronary intervention for complex coronary lesions. *Catheter Cardiovasc Interv.* 2017;
30. Alaswad K, Menon R V., Christopoulos G, Lombardi WL, Karpaliotis D, Grantham JA, et al. Transradial approach for coronary chronic total occlusion interventions: Insights from a contemporary multicenter registry. *Catheter Cardiovasc Interv.* 2015;
31. Watt J, Austin D, Mackay D, Nolan J, Oldroyd KG. Radial Versus Femoral Access for Rotational Atherectomy: A UK Observational Study of 8622 Patients. *Circ Cardiovasc Interv.* 2017;
32. Doyle BJ, Ting HH, Bell MR, Lennon RJ, Mathew V, Singh M, et al. Major Femoral Bleeding Complications After Percutaneous Coronary Intervention. Incidence, Predictors, and Impact on Long-Term Survival Among 17,901 Patients Treated at the Mayo Clinic From 1994 to 2005. *JACC Cardiovasc Interv.* 2008;
33. Goel PK, Jatain S, Khanna R, Pandey CM. Left main PCI: An observational analysis from large single-centre experience. *Indian Heart J.* 2016;
34. Gorol J, Tajstra M, Hudzik B, Lekston A, Gąsior M. Comparison of outcomes in patients undergoing rotational atherectomy after unsuccessful coronary angioplasty versus elective rotational atherectomy. *Postep w Kardiol Interwencyjnej.* 2018;
35. Maeremans J, Palmers PJ, Dens J. Initial experience and feasibility of the new low-profile stingray catheter as part of the antegrade dissection and re-entry revascularization strategy for coronary chronic total occlusions. *Am J Case Rep.* 2017;
36. Yin WH, Tseng CK, Tsao TP, Jen HL, Huang WP, Huang CL, et al. Transradial versus transfemoral rotablation for heavily calcified coronary lesions in contemporary drug-eluting stent era. *J Geriatr Cardiol.* 2015;
37. Yang YJ, Kandzari DE, Gao Z, Xu B, Chen JL, Qiao S Bin, et al. Transradial versus transfemoral method of percutaneous coronary revascularization for unprotected left main coronary artery disease: Comparison of procedural and late-term outcomes. *JACC Cardiovasc Interv.* 2010;
38. Bernat I, Aminian A, Pancholy S, Mamas M, Gaudino M, Nolan J, et al. Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention: An International Consensus Paper. *JACC: Cardiovascular Interventions.* 2019.
39. Saito S, Ikei H, Hosokawa G, Tanaka S. Influence of the ratio between radial artery inner diameter and sheath outer diameter on radial artery flow after transradial coronary intervention. *Catheter Cardiovasc Interv.* 1999;
40. Kotowycz MA, Džavík V. Radial artery patency after transradial catheterization. *Circ Cardiovasc Interv.* 2012;
41. Rademakers LM, Laarman GJ. Critical hand ischaemia after transradial cardiac catheterisation: An uncommon complication of a common procedure. *Netherlands Hear J.* 2012;
42. Ayan M, Smer A, Azzouz M, Abuzaid A, Mooss A. Hand ischemia after transradial coronary angiography: Resulting in right ring finger amputation. *Cardiovasc Revascularization Med.* 2015;
43. Amin H. Prevention of radial artery occlusion: It's the right thing to do. *EuroIntervention.* 2015;
44. Kiemeneij F, Yoshimachi F, Matsukage T, Amoroso G, Fraser D, Claessen BE, et al. Focus on maximal miniaturisation of transradial coronary access materials and techniques by the Slender Club Japan and Europe: An overview and classification. *EuroIntervention.* 2015.
45. Mamas MA, Fath-Ordoubadi F, Fraser DG. Atraumatic complex transradial

- 1
2
3 intervention using large bore sheathless guide catheter. *Catheter Cardiovasc Interv.*
4 2008;
- 5 46. Fraser D, Mamas MA. Transradial Sheathless Approach for PCI. *Current Cardiology*
6 *Reports.* 2015.
- 7 47. Horie K, Tada N, Isawa T, Matsumoto T, Taguri M, Kato S, et al. A randomised
8 comparison of incidence of radial artery occlusion and symptomatic radial artery spasm
9 associated with elective transradial coronary intervention using 6.5 Fr SheathLess
10 Eaucath Guiding Catheter vs. 6.0 Fr Glidesheath Slender. In: *EuroIntervention.* 2018.
- 11 48. Mohsen A, Alqasrawi M, Shantha GPS, DeZorzi C, Panaich S. Comparison of Radial
12 Artery Occlusion Following Transradial Access for Percutaneous Coronary
13 Intervention Using Sheath-based versus Sheathless Technique. *Sci Rep.* 2018;
- 14 49. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis
15 in myocardial infarction (TIMI) trial, phase I: A comparison between intravenous
16 tissue plasminogen activator and intravenous streptokinase. Clinical findings through
17 hospital discharge. *Circulation.* 1987;
- 18 50. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute
19 Myocardial Infarction. *N Engl J Med.* 1993;
- 20 51. White HD, Aylward PE, Gallo R, Bode C, Steg G, Steinhubl SR, et al. Hematomas of
21 at least 5 cm and outcomes in patients undergoing elective percutaneous coronary
22 intervention: Insights from the SafeTy and Efficacy of Enoxaparin in PCI patients, an
23 international randomized Evaluation (STEEPLE) trial. *Am Heart J.* 2010;
- 24 52. van Leeuwen MAH, Hollander MR, van der Heijden DJ, van de Ven PM, Opmeer
25 KHM, Taverne YJHJ, et al. The ACRA Anatomy Study (Assessment of Disability
26 After Coronary Procedures Using Radial Access): A Comprehensive Anatomic and
27 Functional Assessment of the Vasculature of the Hand and Relation to Outcome After
28 Transradial Catheterization. *Circ Cardiovasc Interv.* 2017;
- 29 53. Ul Haq MA, Rashid M, Kwok CS, Wong CW, Nolan J, Mamas MA. Hand dysfunction
30 after transradial artery catheterization for coronary procedures. *World J Cardiol.* 2017;
- 31 54. Ijsselmuiden A, Zwaan E, Kofflard M, Holtzer C. TCT-639 Upper extremity function
32 after transradial PCI: preliminary long term results of the ARCUS trial. *J Am Coll*
33 *Cardiol.* 2017;
- 34 55. Zwaan EM, Koopman AGMM, Holtzer CAJ, Zijlstra F, Ritt MJPF, Amoroso G, et al.
35 Revealing the impact of local access-site complications and upper extremity
36 dysfunction post transradial percutaneous coronary procedures. *Netherlands Heart*
37 *Journal.* 2015.
- 38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



miro

Figure 1: enrollment flowchart of the COLOR trial

300x413mm (72 x 72 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P
	2b	All items from the World Health Organization Trial Registration Data Set	P 3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	P 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P 1
	5b	Name and contact information for the trial sponsor	P 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P 4
	6b	Explanation for choice of comparators	P 4
Objectives	7	Specific objectives or hypotheses	P 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P 4

Methods: Participants, interventions, and outcomes

1			
2			
3			
4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
5			P 4
6			
7			
8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
9			P 5
10			
11			
12			
13	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
14			P 6
15			
16		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
17			N/A
18			
19			
20		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
21			N/A
22			
23			
24			
25		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
26			N/A
27			
28	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
29			P 5
30			
31			
32			
33			
34			
35			
36	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
37			Fig. 1
38			
39			
40			
41	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
42			P 6
43			
44			
45	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
46			P 6
47			

Methods: Assignment of interventions (for controlled trials)

Allocation:

51			
52			
53	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
54			P 6
55			
56			
57			
58			
59			
60			

1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	N/A
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	N/A
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	N/A
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13		17b	If blinded, circumstances under which unblinding is permissible, and	N/A
14			procedure for revealing a participant's allocated intervention during	
15			the trial	
16				
17				
18				
19				
20	Methods: Data collection, management, and analysis			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	P11-12
22	methods		trial data, including any related processes to promote data quality (eg,	
23			duplicate measurements, training of assessors) and a description of	
24			study instruments (eg, questionnaires, laboratory tests) along with	
25			their reliability and validity, if known. Reference to where data	
26			collection forms can be found, if not in the protocol	
27		18b	Plans to promote participant retention and complete follow-up,	P 6
28			including list of any outcome data to be collected for participants who	
29			discontinue or deviate from intervention protocols	
30	Data	19	Plans for data entry, coding, security, and storage, including any	P 6
31	management		related processes to promote data quality (eg, double data entry;	
32			range checks for data values). Reference to where details of data	
33			management procedures can be found, if not in the protocol	
34	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	P 6
35	methods		Reference to where other details of the statistical analysis plan can be	
36			found, if not in the protocol	
37		20b	Methods for any additional analyses (eg, subgroup and adjusted	N/A
38			analyses)	
39		20c	Definition of analysis population relating to protocol non-adherence	N/A
40			(eg, as randomised analysis), and any statistical methods to handle	
41			missing data (eg, multiple imputation)	
42				
43				
44				
45				
46				
47				
48				
49				
50				
51				
52	Methods: Monitoring			
53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	N/A
54			and reporting structure; statement of whether it is independent from	
55			the sponsor and competing interests; and reference to where further	
56			details about its charter can be found, if not in the protocol.	
57			Alternatively, an explanation of why a DMC is not needed	
58				
59				
60				

1		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
2				
3				
4				
5				
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P 4
7				
8				
9				
10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
12				
13				
14				
15	Ethics and dissemination			
16				
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	N/A
18				
19				
20				
21	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
22				
23				
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A
27				
28				
29				
30		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
31				
32				
33	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A
34				
35				
36				
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P 1
38				
39				
40	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
41				
42				
43				
44				
45	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
46				
47				
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P 7
49				
50				
51				
52				
53				
54		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
55				
56				
57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
58				
59				
60				

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

For peer review only

BMJ Open

Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR trial study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038042.R1
Article Type:	Protocol
Date Submitted by the Author:	14-May-2020
Complete List of Authors:	Meijers, Thomas; Isala Hospitals, Cardiology Aminian, Adel ; Centre Hospitalier Universitaire de Charleroi, Cardiology Teeuwen, Koen; Catharina Hospital, Cardiology van Wely, Marleen; Radboudumc, Cardiology Schmitz, Thomas; Elisabeth-Krankenhaus-Essen GmbH, Cardiology Dirksen, Maurits; Noordwest Ziekenhuisgroep, Cardiology van der Schaaf, Rene; OLVG, Cardiology Iglesias, Juan; Geneva University Hospitals, Cardiology Agostoni, Pierfrancesco; ZNA, Cardiology Dens, Joseph; Ziekenhuis Oost-Limburg, Cardiology Knaapen, Paul; Amsterdam UMC - Locatie VUMC, Cardiology Rathore, Sudhir; Frimley Health NHS Foundation Trust, Cardiology Ottervanger, Jan Paul; Isala Hospitals, Cardiology Dambrink, Jan-Henk; Isala Hospitals, Cardiology Roolvink, Vincent; Isala Hospitals, Cardiology Gosselink, Marcel; Isala Hospitals, Cardiology Hermanides, Renicus; Isala Hospitals, Cardiology van Royen, Niels; Radboudumc, Cardiology van Leeuwen, Maarten; Isala Hospitals, Cardiology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	Coronary intervention < CARDIOLOGY, CARDIOLOGY, Coronary heart disease < CARDIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1
5 2 Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR
6 3 trial study protocol
7 4
8 5

9 6 Thomas A. Meijers MD^{a*}, Adel Aminian MD^{b*}, Koen Teeuwen MD, PhD^c, Marleen van
10 7 Wely MD^d, Thomas Schmitz MD, PhD^e, Maurits T. Dirksen MD, PhD^f, René J. van der
11 8 Schaaf MD, PhD^g, Juan F. Iglesias MD, PhD^h, Pierfrancesco Agostoni MD, PhDⁱ, Joseph
12 9 Dens MD, PhD^j, Paul Knaapen MD, PhD^k, Sudhir Rathore MD, FRCP^l, Jan Paul Ottervanger
13 10 MD, PhD^a, Jan Henk E. Dambrink MD, PhD^a Vincent Roolvink MD, PhD^a, A.T. Marcel
14 11 Gosselink MD, PhD^a, Renicus S. Hermanides MD, PhD^a, Niels van Royen MD, PhD^d,
15 12 Maarten A.H. van Leeuwen MD, PhD^a

16 13
17 14
18 14 * Both authors contributed equally.
19 15

20 16 Word count: 3475
21 17

22 18 Departments and institutions

23 19 ^a Department of Cardiology, Isala Heart Center, Zwolle, the Netherlands

24 20 ^b Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi,
25 21 Belgium

26 22 ^c Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands

27 23 ^d Department of Cardiology, Radboud University Medical Center, Nijmegen, the
28 24 Netherlands

29 25 ^e Department of Cardiology, Elisabeth Krankenhaus, Essen, Germany

30 26 ^f Department of Cardiology, Northwest Clinics, Alkmaar, the Netherlands

31 27 ^g Department of Cardiology, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the
32 28 Netherlands

33 29 ^h Department of Cardiology, Geneva University Hospital, Geneva, Switzerland

34 30 ⁱ Department of Cardiology, ZNA Middelheim, Antwerp, the Netherlands

35 31 ^j Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium

36 32 ^k Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands

37 33 ^l Department of Cardiology, Frimley Health NHS Foundation Trust, Surrey, United
38 34 Kingdom
39 35

40 36 Sources of funding

41 37 Terumo EMEA (Leuven, Belgium) supported this investigator-initiated study by an
42 38 unrestricted grant.
43 39

44 40 Conflict of interest

45 41 Maarten A.H. van Leeuwen, Adel Aminian and and Juan F. Iglesias are consultants for
46 42 Terumo corp., Juan F. Iglesias and Thomas Schmitz have received honoraria/speakers fee for
47 43 Terumo corp., the other authors have no conflicts of interest to declare.
48 44

49 45 Clinical trial registration

50 46 ClinicalTrials.gov identifier: NCT03846752.
51 47

52 48 Address for correspondence

53 49 dr. M.A.H. van Leeuwen, Isala Heart Center, Dr. van Heesweg 2, 8025 AB Zwolle, The
54 50 Netherlands. Email: m.a.h.van.leeuwen@isala.nl
55 51
56 52
57 53
58 54
59 55
60 56

Abstract**Introduction**

The radial artery has become the standard access site for percutaneous coronary intervention (PCI) in stable coronary artery disease and acute coronary syndrome, because of less access site related bleeding complications. Patients with complex coronary lesions are underrepresented in randomized trials comparing radial with femoral access with regard to safety and efficacy. The femoral artery is currently the most applied access site in patients with complex coronary lesions, especially when large bore guiding catheters are required. With slender technology, transradial PCI may be increasingly applied in patients with complex coronary lesions when large bore guiding catheters are mandatory and might be a safer alternative as compared to the transfemoral approach.

Methods and analysis

A total of 388 patients undergoing complex PCI will be randomized to radial 7 French access with Terumo Glidesheath Slender (Terumo Corp., Japan) or femoral 7 French access as comparator. The primary outcome is the incidence of the composite end-point of clinically relevant access site related bleeding and/or vascular complications requiring intervention. Procedural success and major adverse cardiovascular events up to 1 month will also be compared between both groups.

Ethics and dissemination

Ethical approval for the study was granted by the local Ethics Committee at each recruiting center. The trial outcomes will be published in peer-reviewed journals of the concerned literature. The COLOR trial has been administered in the ClinicalTrials.gov database, reference number: NCT03846752.

Strengths and limitations of this study

- The design as a randomized 1:1 open label study (radial 7 Fr versus femoral 7) and the vast experience with complex PCI of the participating centers
- Clinical Event Committee adjudicated and clinically relevant primary endpoint
- First study assessing extremity dysfunction after complex large bore PCI
- As a limitation, bias could be derived from the unblinded nature of the study for the treating interventional cardiologist
- As a limitation, use of secondary access sites for hybrid approach of CTO lesions will influence efficacy outcomes, although it will not influence the primary endpoint.

Keywords

Complex percutaneous coronary intervention - Chronic total occlusion - Radial access - Femoral access - Slender

Abbreviations

PCI = percutaneous coronary intervention

CTO = chronic total occlusion

CABG = coronary artery bypass grafting

ACS = acute coronary syndrome

BARC = bleeding academic research consortium

MACE = major adverse cardiovascular events

AE = adverse event

SAE = serious adverse event

TR= transradial

1
2
3 101 TRA= transradial access
4 102 TF = transfemoral
5 103 TFA = transfemoral access
6 104 Fr = French
7
8 105
9 106
10 107
11 108
12 109
13 110
14 111
15 112
16 113
17 114
18 115
19 116
20 117
21 118
22 119
23 120
24 121
25 122
26 123
27 124
28 125
29 126
30 127
31 128
32 129
33 130
34 131
35 132
36 133
37 134
38 135
39 136
40 137
41 138
42 139
43 140
44 141
45 142
46 143
47 144
48 145
49 146
50 147
51 148
52 149
53 150
54
55
56
57
58
59
60

For peer review only

151 **Background**

152 The radial artery has become the standard access site for percutaneous coronary interventions
153 (PCI), driven not only by lower rates of major bleeding and vascular complications, but also
154 by reduced mortality in patients presenting with acute coronary syndrome (ACS) (1–3). This
155 has led the 2018 ESC/EACTS Guidelines on myocardial revascularization to recommend
156 transradial access (TRA) over transfemoral access (TFA) as a class Ia indication in ACS
157 patients undergoing invasive management (4). In patients with stable coronary artery disease,
158 several small randomized trials comparing radial and femoral access have shown significantly
159 less bleeding in favor of radial access but no mortality benefit (5–7). Of note, patients with
160 complex coronary lesions were not included in these trials or not specifically described. PCI
161 of chronic total occlusions (CTO), left main disease, heavily calcified or complex bifurcation
162 lesions often require the use of large-bore guiding catheters (7 Fr or larger inner diameter).
163 Indeed, large-bore guiding catheters provide more back-up and stability in addition to better
164 materials' compatibility, leading to higher procedural success rates in more complex lesions
165 (8,9). Because of potential radial artery-sheath mismatch, spasms or back-up problems, the
166 femoral artery is still the most applied access site for complex PCI (10,11). In return, TFA
167 with increased sheath size is associated with bleeding and vascular complications and adverse
168 clinical outcome, including myocardial infarction (MI), stroke and death (12,13). The recent
169 availability of modern slender technology, such as the thin-walled radial introducer sheath
170 (Glidesheath Slender®, Terumo Corp., Japan), has the potential to expand the use of TRA for
171 complex PCI. As compared to the average outer diameter of a standard sheath, the outer
172 diameter of these slender sheaths has been reduced by approximately 1 Fr while maintaining
173 the inner-diameter equivalent. In a prospective single-arm study it was recently shown that
174 complex transradial (TR) PCI with a 7 Fr Glidesheath Slender is safe and effective (14).
175 Several observational studies have been published describing feasibility of large bore TRA for
176 PCI of CTO's, left main disease, heavily calcified lesions and complex bifurcations without
177 affecting procedural success rates (9,11,15–18). However, randomized data comparing TRA
178 and TFA for percutaneous treatment of complex coronary lesions are lacking. Therefore, we
179 have designed a randomized study, comparing the safety and efficacy of TRA and TFA for
180 complex PCI using large-bore guiding catheters.

181 **Methods**

182 *Study design*

183 The Complex Large-Bore Radial PCI (COLOR) trial is an investigator-initiated international
184 multi-center study with a prospective, randomized controlled design. Participating centers are
185 the Isala Heart Center (Zwolle, the Netherlands), Catharina Hospital (Eindhoven, the
186 Netherlands), Radboud University Medical Center (Nijmegen, The Netherlands), Elisabeth-
187 Krankenhaus (Essen, Germany), NorthWest Clinics (Alkmaar, the Netherlands), Onze Lieve
188 Vrouwe Gasthuis Hospital (Amsterdam, the Netherlands), Centre Hospitalier Universitaire de
189 Charleroi (Charleroi, Belgium), ZNA Middelheim (Antwerpen, Belgium), Hospital Oost-
190 Limburg (Genk, Belgium), Geneva University Hospital (Geneva, Switzerland), VU
191 University Medical Center (Amsterdam, The Netherlands) and Frimley NHS (Surrey, United
192 Kingdom). All centers have been selected based on their high volumes and experience with
193 complex PCI and large bore access. For CTO, each center has a dedicated program for an
194 average of 6 years, with 1-3 dedicated CTO operators and an average of 110 procedures per
195 year (spreading from 55 to 200 procedures per year). 83% of CTO procedures are done with
196 dual arterial access, with biradial access in 20%, bifemoral access in 24% and radial/femoral
197 (hybrid) access in the remaining 49% of cases. Large bore access is used in 89% of cases. For
198 non-CTO complex PCI, the participating centers have a dedicated program for an average of
199 11 years, performing an average of 245 procedures per year with 3-5 complex PCI operators.

201 76% of these cases are done with TRA and 24% with TFA. Large bore access is used in 62%
202 of all complex non CTO PCI.

203 204 *Trial organization*

205 The trial is approved by the appropriate ethics review board at each clinical site. Written
206 informed consent will be obtained from all patients before enrollment. The trial was designed
207 in accordance with the declaration of Helsinki. All data will be collected in an electronic data
208 capturing system, the eDREAM (electronic case record form Diagnostic REsearch And
209 Management). Diagram BV, Zwolle, the Netherlands will be responsible for overall trial and
210 data management, as well as monitoring of the study. Evaluation of serious adverse events is
211 being performed by an independent Data Safety Monitoring Board (DSMB). A Clinical
212 Events Committee (CEC) will review and adjudicate all end-point related adverse events. The
213 COLOR trial has been administered in the ClinicalTrials.gov database, reference number:
214 NCT03846752.

215 216 *Objectives*

217 The primary objective of this study is to investigate whether TR PCI is superior to
218 transfemoral (TF) PCI in complex coronary lesions with large-bore guiding catheters with
219 respect to clinically relevant access site related bleeding and/or vascular complications.

220
221 As secondary objectives, TR and TF large-bore access will be compared with regard to
222 procedural success, procedural time, fluoroscopy time, contrast use, crossover rates, major
223 adverse cardiovascular events (MACE) and non-access site related bleeding or vascular
224 complications for complex PCI.

225
226 For exploratory purposes extremity dysfunction and discomfort will be compared between TR
227 and TF treated patients for complex PCI with large-bore guiding catheters.

228 229 *Inclusion*

230 All patients of 18 years or older, presenting with stable coronary artery disease, unstable
231 angina or non-ST elevation myocardial infarction and planned for complex PCI of CTO
232 (defined as lesion exhibiting TIMI 0-1 flow in a native coronary artery with an occlusion
233 duration of ≥ 3 months), left main, complex bifurcation or heavy calcification, in whom the
234 operator anticipates that a 7 Fr guiding catheter is indicated, are screened for inclusion.
235 Patients with ST elevation myocardial infarction or cardiogenic shock will be excluded.
236 Patients with contraindications for femoral or radial access, such as occlusive peripheral
237 artery disease, known severe spasm or known anatomical variants prohibiting radial or
238 femoral access on both sides will be excluded as well. See also Figure 1 for graphic
239 representation of study inclusion.

240 241 *Randomization*

242 After providing written informed consent, eligible subjects are randomly assigned to receive
243 one of the two study treatments in a 1:1 ratio. Treatment assignments are performed centrally
244 through a dedicated website as part of the electronic Case Report Form (eCRF) according to a
245 computer-generated random schedule in random permuted blocks with stratification by site
246 (19). There will be no blinding of the randomization assignment.

247 248 *Endpoints*

249 Clinically relevant access site related bleeding or vascular complication requiring intervention
250 of the randomized access site during hospitalization is defined as primary endpoint. Bleeding

1
2
3 251 will be classified according to the Bleeding Academic Research Consortium (BARC) criteria
4 252 (20), and considered clinically relevant when the score is ≥ 2 (CEC adjudicated)(21). Severity
5 253 and type of intervention of vascular complications is specified in the CEC manual
6 254 (Supplementary file I).

7 255 Secondary safety and efficacy endpoints are:

- 8 256 - Procedural success (defined as successful PCI of the target lesion with a residual stenosis of
9 257 less than 20%, without in-hospital MACE), procedural time, fluoroscopy time, contrast use
10 258 and crossover rate (crossover is defined as conversion from TF to TR or vice versa;
11 259 conversion to contralateral TR or TF access site is not considered crossover).
12 260 - Clinically relevant BARC bleedings or vascular complications (requiring intervention) that
13 261 are not related to the randomized access (CEC adjudicated)
14 262 - MACE, defined as composite of death, MI and repeat revascularization, during
15 263 hospitalization and at 1 month (CEC adjudicated)
16 264

17 265 *Index percutaneous coronary intervention and hospitalization*

18 266 Radial access will be performed according to the local protocol, using direct needle technique
19 267 or venous cannula technique, followed by introduction of a 7 Fr Glidesheath Slender. A
20 268 standard cocktail of nitroglycerine and verapamil will be given intra-arterially after radial
21 269 sheath placement. Femoral access will be performed using direct needle technique, followed
22 270 by introduction of a standard 7 Fr femoral sheath. Use of ultrasound for vascular access will
23 271 be left to the operator's discretion. A bolus of unfractionated heparin will be given after
24 272 sheath placement, adapted to the patient's body weight. Activated clotting time (ACT)
25 273 measurements will be performed during the procedure according to local protocol. Additional
26 274 arterial access will be left to the discretion of the operator, i.e. in case of double arterial access
27 275 for hybrid CTO treatment. PCI will be performed according to standard procedures with
28 276 modern drug eluting stents. The applied technique for complex PCI will be left to the
29 277 discretion of the operator. Patent hemostasis after radial access with the reverse Barbeau test
30 278 is highly recommended (22). The type of femoral artery hemostasis will be left to the
31 279 discretion of the treating interventional cardiologist; however the application of a closure
32 280 device is advocated. The visual analogue scale (VAS) will be used to assess post-procedural
33 281 pain of the access site(s). Before discharge the access site(s) will be checked for bleeding and
34 282 vascular complications. Radial artery patency will be checked with the reverse Barbeau test
35 283 (22). Additional ultrasound or doppler will be performed in those patients with suspected
36 284 radial or femoral occlusion or the presence of other vascular complications.
37 285

38 286 *Extremity dysfunction*

39 287 Two validated questionnaires will be used to assess the occurrence of upper and lower
40 288 extremity dysfunction. Upper extremity function will be measured with the QuickDASH
41 289 (Quick Disabilities of Arm, Shoulder and Hand) score (23) measured at baseline (before PCI)
42 290 and at 1 month follow-up. Lower extremity function will be measured with the LEFS (Lower
43 291 Extremity Functional Scale) (24). Both questionnaires are valid, reliable and responsive to
44 292 monitor and assess pain and function of the extremities.
45 293

46 294 *Follow-up*

47 295 Follow-up will be performed 1 month after index procedure discharge by either phone call or
48 296 outpatient clinic visit. MACE and access site bleeding or vascular complications will be
49 297 documented. Extremity function and discomfort will be assessed, using the aforementioned
50 298 scores. Adverse Events (AE's) will be monitored from inclusion to one-month follow-up and
51 299 will be assessed by an independent DSMB, composed of two experienced cardiologists and
52 300 one statistician, reviewing patient safety and study integrity.

301 *Sample size calculation and statistics*

302 Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the
303 proportion of access site related bleeding or vascular complication to be 3.5% with radial
304 access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1)
305 will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients
306 will be needed. Data will be analyzed according to the intention-to-treat analysis. All
307 statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically
308 significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago,
309 Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-
310 Square test will also be used for our secondary objectives with binary outcomes. For our
311 secondary objectives with continuous variables we will use the Student's t-test (normally
312 distributed) or the Mann-Whitney U test (non-normally distributed). A pre-specified battery
313 of sub-group analyses will be performed as well, including several independent risk factors
314 for clinically significant bleeding and vascular complications. For demographics and baseline
315 characteristics, these sub-groups consist of age ≥ 75 years, female sex, low body weight
316 (Body Mass Index < 18.5), hypertension, peripheral arterial disease, left ventricular ejection
317 fraction $< 30\%$, severe renal dysfunction (Modification of Diet in Renal Disease (MDRD) $<$
318 $30\text{ml}/1.73\text{m}^2$) and pre-existent anemia (hemoglobin < 6.8 mmol/l) (13,25–30). For procedural
319 characteristics, sub-group analyses will be performed for use of secondary access site,
320 ultrasound guided puncture, ACT > 150 seconds right before sheath removal and use of
321 closure device (31–34). In addition, primary and secondary endpoints will be specified for the
322 entire population as well as for each group of complex lesions separately (CTO, left main
323 disease, complex bifurcation and heavy calcification). Statistical analysis will be performed
324 by an independent contract research organization (Diagram BV, Zwolle, the Netherlands).

325 *Ethics and dissemination*

326 Ethical approval for the study was granted by the local Ethics Committee ('Medisch Ethische
327 Toetsing Commissie Isala Zwolle' for all Dutch sites, 'Commissie voor medische ethiek
328 ZNA' for ZNA Middelheim, 'Comité Medische Ethiek Ziekenhuis Oost-Limburg' for
329 Hospital Oost-Limburg, 'Comité d'éthique CHU-Charleroi – ISPPC' for Centre Hospitalier
330 Universitaire de Charleroi, 'Commission cantonale d'éthique de la recherche CCER –
331 Republique et Canton de Geneve' for Geneva University Hospital, 'Ethik Kommission de
332 Ärztekammer Nordrhein' for Elisabeth-Krankenhaus and 'Riverside Research Ethics
333 Committee' for Frimley NHS) after reviewing the protocol, site-
334 specific informed consentforms (local language and English versions, see also supplementary
335 file II), participant education and recruitment materials, other requested documents and any
336 subsequent modifications. Trained research nurses or physicians directly involved in the trial
337 will introduce the trial to eligible patients. Patients will also receive patient information
338 form (PIF). The research nurse or physician will discuss the trial with patients in light of the
339 information provided in the PIF and will obtain written consent from patients willing to
340 participate in the trial. No reimbursement is provided to study participants. All study-related
341 information will be stored securely at the study site. All participant information will be stored
342 in locked file cabinets in areas with limited access. All reports, data collection, process, and
343 administrative forms will be identified by a coded identification-number only to maintain
344 participant confidentiality. All records that contain names or other personal identifiers, such
345 as locator forms and informed consent forms, will be stored separately from study records
346 identified by code number. All local databases will be secured with password-protected
347 access systems. Safety and progress reports to the EC's will be made at least annually and
348 within three months of study termination or completion. These reports will include the total
349 number of participants enrolled and summaries of the DSMB. Any modifications to the
350

1
2
3 351 protocol which may have impact on the conduct of the study, potential benefit of the patient
4 352 or may affect patient safety, including changes of study objectives, study design, patient
5 353 population, sample sizes, study procedures, or significant administrative aspects will require a
6 354 formal amendment to the protocol. Such amendment will have to be approved by the Ethics
7 355 Committee prior to implementation. The study findings will be disseminated via publication
8 356 of peer-reviewed manuscripts and presentations at international conferences, as well as
9 357 through media publications. Results will be published irrespective of whether the findings are
10 358 positive or negative.

11 359

12 360 *Patient and Public Involvement*

13 361 No patient involved

14 362

15 363 **Discussion**

16 364 TRA is nowadays the standard for PCI, mainly driven by the lower risk of bleeding and
17 365 vascular complications compared to TFA, with even a mortality benefit in ACS patients
18 366 (2,3,35,36). Randomized data in patients with stable coronary artery disease are limited and
19 367 more heterogeneous, and show less beneficial effect of radial over femoral access (1,37,38).
20 368 Moreover, complex coronary lesions are absent or at least not specifically described in most
21 369 trials supporting current guidelines on myocardial revascularization. Currently, the femoral
22 370 artery is still considered the preferred access site for complex PCI by many operators
23 371 (11,16,39–41), despite the increased risk of bleeding and vascular complications, especially
24 372 when large bore guiding catheters (≥ 7 Fr) are required (11,42–45). During CTO-PCI, the use
25 373 of large-bore guiding catheters has been reported in 60-70% of cases and is associated with a
26 374 higher procedural success rate (9,16). Large-bore guiding catheters have better materials'
27 375 compatibility, especially when using guide extensions and microcatheters. The use of
28 376 CrossBoss/Stingray (Boston Scientific, Marlborough, MA, USA) for antegrade dissection/re-
29 377 entry technique is only possible with large-bore guiding catheters (46). Although registries
30 378 show increased temporal adoption of TRA for PCI of heavily calcified lesions with use of
31 379 rotational atherectomy with similar procedural success rates and less bleeding, TFA is still
32 380 used in a large proportion of these procedures, which often mandate large bore guiding
33 381 catheters especially for accommodating larger burr sizes (47,48). Application of large-bore
34 382 guiding catheters for complex PCI of left main and true bifurcations is advocated by experts,
35 383 though efficacy and safety data are lacking. Limited data show comparable feasibility of TRA
36 384 versus TFA for left main as well as bifurcation PCI with a tendency towards less bleeding
37 385 complications (11,49–55).

38 386

39 387 The most important argument to refrain from TR PCI for complex coronary lesions is the
40 388 limited diameter of the radial artery. Current standard 7 Fr radial sheaths have an outer
41 389 diameter of 2.97-3.19 mm (56). As such, the percentage of patients with a radial artery
42 390 smaller than the outer diameter of a 7 Fr sheath ranges between 29% and 67% in men and
43 391 between 60% up to 85% in women (57). This suggests that using a standard 7 Fr sheath for
44 392 TRA will result in sheath to artery mismatch in a significant proportion of patients, increasing
45 393 the risk of vascular complications. Radial artery occlusion (RAO) is the most frequent
46 394 complication after radial access, with increasing RAO rates with increasing sheath size (58).
47 395 In most instances, RAO will not lead to any clinical sequelae, however in rare cases RAO
48 396 may require intervention because of extremity dysfunction or ischemia (59,60). Moreover,
49 397 RAO prohibits future re-cannulation of the radial artery, harvesting the radial artery as
50 398 conduit for CABG or creating a hemodialysis shunt (61). Other arguments to use the femoral
51 399 artery for complex PCI have been suggested, such as improved back-up with potential higher

52 60

1
2
3 400 procedural success rates and shorter procedural time and lower radiation dose. However, this
4 401 is not supported by observational data showing similar effectiveness, procedural success rates,
5 402 cross-over rates, radiation dose and contrast use for TRA and TFA (11,16,17,39).
6 403 Several technologies have been developed to facilitate large bore access through the radial
7 404 artery (62). A sheathless approach for example was shown to be a feasible alternative for
8 405 large bore radial access (63). The 7.5 Fr Eaucath sheathless guiding catheter (ASAHI Intecc,
9 406 Aichi, Japan) has the same inner diameter as a regular 7 Fr guiding catheter, but an outer
10 407 diameter of 2.49 mm, resulting in a large reduction in outer diameter (approximately 2 Fr)
11 408 compared with a standard 7 Fr sheath (64). However, PCI with sheathless guiding catheters
12 409 requires specific experience due to the highly hydrophilic coating, and limited evidence exists
13 410 regarding the true impact on RAO (65,66). Miniaturization of TR equipment can also be
14 411 achieved through a sheath-based approach. Thanks to a reduction in sheath wall thickness
15 412 (“slender technology”), thin-walled sheaths have reduced their outer diameter while
16 413 maintaining the same inner diameter. The 7 Fr Glidesheath Slender (Terumo, Japan) is the
17 414 first commercially available 7 Fr thin-walled sheath, combining an inner diameter of 2.46mm,
18 415 compatible with any 7 Fr guiding catheter, with a reduced outer diameter of 2.79mm. A recent
19 416 prospective multicenter study has shown the feasibility and safety of using the 7 Fr
20 417 Glidesheath Slender for complex TR-PCI in daily practice with a high rate of procedural
21 418 success and low rate of vascular complications (14).
22 419

23 420 In the literature, several outcome measures have been used to evaluate access site related
24 421 bleeding complications, such as the Thrombolysis in Myocardial Infarction (TIMI)(67), the
25 422 Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary
26 423 arteries (GUSTO)(68) or BARC (20). Access site hematoma size has also been used as an
27 424 outcome measure in studies comparing radial with femoral access. BARC bleeding ≥ 2 has
28 425 shown to independently predict 1-year mortality and capture more clinically significant
29 426 bleeding than TIMI minor/major and GUSTO moderate/severe criteria (20,21). Importantly,
30 427 hematoma size alone, not meeting criteria for other bleeding outcome measures, has not
31 428 shown any association with clinically relevant endpoints (69). The current trial will use the
32 429 BARC bleeding score for the primary outcome measure to detect a clinically relevant
33 430 difference in bleedings between TRA and TFA for complex PCI, adjudicated by a CEC.
34 431 Besides bleeding and vascular complications, vascular access may also have a potential effect
35 432 on extremity function (70,71). Although upper extremity dysfunction is present in a small
36 433 proportion of patients after TRA, it can lead to important morbidity for the affected patients
37 434 (70–73). Extremity dysfunction may be more pronounced in patients with large-bore access.
38 435 In addition, current literature does not provide an insight around prevalence and significance
39 436 of lower extremity function after TFA (71). Therefore, we will assess the occurrence of
40 437 extremity dysfunction utilizing the QuickDASH and LEFS questionnaires, which will be
41 438 valuable information for both patients and doctors.
42 439

43 440 In conclusion, The COLOR trial is the first prospective multicenter randomized trial
44 441 comparing TRA with TFA using large-bore guiding catheters for complex PCI. Currently 290
45 442 patients are randomized. The results of this trial will provide important insights about the
46 443 safety and efficacy of large-bore TRA and TFA for complex PCI, with a potential impact on
47 444 daily practice.
48 445
49 446
50 447
51 448
52 449

Contributorship statement

Maarten van Leeuwen and Adel Aminian substantially contributed to conception and design of the study protocol. Thomas Meijers, Adel Aminian, Koen Teeuwen, Marleen van Wely, Thomas Schmitz, Rene van der Schaaf, Maurits Dirksen, Juan Iglesias, Pierfrancesco Agostoni, Joseph Dens, Paul Knaapen, Sudhir Rathore and Maarten van Leeuwen contributed to acquisition of data. Thomas Meijers, Adel Aminian and Maarten van Leeuwen contributed to analysis of data. Thomas Meijers, Adel Aminian, Maarten van Leeuwen and Niels van Royen contributed to interpretation of data. Thomas Meijers, Adel Aminian and Maarten van Leeuwen reviewed the literature, contributed to the design and wrote the draft of the manuscript. Thomas Meijers, Adel Aminian, Koen Teeuwen, Marleen van Wely, Thomas Schmitz, René van der Schaaf, Maurits Dirksen, Juan Iglesias, Pierfrancesco Agostoni, Joseph Dens, Paul Knaapen, Sudhir Rathore, Jan Paul Ottervanger, Jan Henk Dambrink, Vincent Roolvink, Marcel Gosselink, Renicus Hermanides, Niels van Royen and Maarten van Leeuwen contributed to refinement of the study protocol and approved the final manuscript.

References

1. Ferrante G, Rao S V., Jüni P, Da Costa BR, Reimers B, Condorelli G, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2016;
2. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet.* 2011;
3. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet.* 2018;
4. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg.* 2019;
5. Ferrante G, Rao S V., Jüni P, Da Costa BR, Reimers B, Condorelli G, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2016;9(14):1419–34.
6. Santos E, Bodí V, Sanchis J, Núñez J, Mainar L, Miñana G, et al. The Left Radial Approach in Daily Practice. A Randomized Study Comparing Femoral and Right and Left Radial Approaches. *Rev Española Cardiol (English Ed.)* 2009;
7. Louvard Y, Benamer H, Garot P, Hildick-Smith D, Loubeyre C, Rigattieri S, et al. Comparison of transradial and transfemoral approaches for coronary angiography and angioplasty in octogenarians (the OCTOPLUS study). *Am J Cardiol.* 2004;
8. Burzotta F, De Vita M, Lefevre T, Tommasino A, Louvard Y, Trani C. Radial approach for percutaneous coronary interventions on chronic total occlusions: Technical issues and data review. *Catheterization and Cardiovascular Interventions.* 2014.
9. Tanaka Y, Moriyama N, Ochiai T, Takada T, Tobita K, Shishido K, et al. Transradial Coronary Interventions for Complex Chronic Total Occlusions. *JACC Cardiovasc Interv.* 2017;

10. Galassi AR, Tomasello SD, Reifart N, Werner GS, Sianos G, Bonnier H, et al. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: Insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. *EuroIntervention*. 2011;
11. Chung S, Her SH, Song PS, Song Y Bin, Hahn JY, Choi JH, et al. Trans-radial versus trans-femoral intervention for the treatment of coronary bifurcations: Results from coronary bifurcation stenting registry. *J Korean Med Sci*. 2013;
12. Smilowitz NR, Kirtane AJ, Guiry M, Gray WA, Dolcimascolo P, Querijero M, et al. Practices and complications of vascular closure devices and manual compression in patients undergoing elective transfemoral coronary procedures. In: *American Journal of Cardiology*. 2012.
13. Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol*. 2003;
14. Aminian A, Iglesias JF, Van Mieghem C, Zuffi A, Ferrara A, Manih R, et al. First prospective multicenter experience with the 7 French Glidesheath slender for complex transradial coronary interventions. *Catheter Cardiovasc Interv*. 2017;
15. Megaly M, Karatasakis A, Abraham B, Jensen J, Saad M, Omer M, et al. Radial Versus Femoral Access in Chronic Total Occlusion Percutaneous Coronary Intervention. *Circ Cardiovasc Interv*. 2019;
16. Jan Bakker E, Maeremans J, Zivelonghi C, Faurie B, Avran A, Walsh S, et al. Fully transradial versus transfemoral approach for percutaneous intervention of coronary chronic total occlusions applying the hybrid algorithm insights from recharge registry. *Circ Cardiovasc Interv*. 2017;
17. De Maria GL, Burzotta F, Trani C, Kassimis G, Pirozzolo G, Patel N, et al. Trends and Outcomes of Radial Approach in Left-Main Bifurcation Percutaneous Coronary Intervention in the Drug-Eluting Stent Era: A Two-Center Registry. *J Invasive Cardiol*. 2015;
18. Rathore S, Hakeem A, Pauriah M, Roberts E, Beaumont A, Morris JL. A comparison of the transradial and the transfemoral approach in chronic total occlusion percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2009;
19. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. *Control Clin Trials*. 1988;
20. Mehran R, Rao S V., Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. *Circulation*. 2011;
21. Vranckx P, White HD, Huang Z, Mahaffey KW, Armstrong PW, Van De Werf F, et al. Validation of BARC Bleeding Criteria in Patients with Acute Coronary Syndromes the TRACER Trial. *J Am Coll Cardiol*. 2016;
22. Wilson SJ, Mitchell A, Gray TJM, Loh HJ, Cruden NL. Patent haemostasis prevents radial artery occlusion in patients with an acute coronary syndrome. *Int J Cardiol*. 2017;
23. Beaton DE, Wright JG, Katz JN, Amadio P, Bombardier C, Cole D, et al. Development of the QuickDASH: COMparison of three item-reduction approaches. *J Bone Jt Surg - Ser A*. 2005;
24. Binkley J, Stratford P, Lott S, Riddle D. The lower extremity functional scale. *Phys Ther*. 1999;
25. Numasawa Y, Kohsaka S, Ueda I, Miyata H, Sawano M, Kawamura A, et al. Incidence and predictors of bleeding complications after percutaneous coronary intervention. *J Cardiol*. 2017;

- 1
2
3 550 26. Numasawa Y, Kohsaka S, Miyata H, Kawamura A, Noma S, Suzuki M, et al. Impact of
4 551 body mass index on in-hospital complications in patients undergoing percutaneous
5 552 coronary intervention in a Japanese real-world multicenter registry. *PLoS One*. 2015;
6 553 27. Singh M, Lennon RJ, Darbar D, Gersh BJ, Holmes DR, Rihal CS. Effect of peripheral
7 554 arterial disease in patients undergoing percutaneous coronary intervention with
8 555 intracoronary stents. *Mayo Clin Proc*. 2004;
9 556 28. Ndrepepa G, Groha P, Lahmann AL, Lohaus R, Cassese S, Schulz-Schüpke S, et al.
10 557 Increased bleeding risk during percutaneous coronary interventions by arterial
11 558 hypertension. *Catheter Cardiovasc Interv*. 2016;
12 559 29. Mamas MA, Anderson SG, O’Kane PD, Keavney B, Nolan J, Oldroyd KG, et al.
13 560 Impact of left ventricular function in relation to procedural outcomes following
14 561 percutaneous coronary intervention: Insights from the British Cardiovascular
15 562 Intervention Society. *Eur Heart J*. 2014;
16 563 30. Urban P, Mehran R, Collieran R, Angiolillo DJ, Byrne RA, Capodanno D, et al.
17 564 Defining high bleeding risk in patients undergoing percutaneous coronary intervention:
18 565 a consensus document from the Academic Research Consortium for High Bleeding
19 566 Risk. *European Heart Journal*. 2019.
20 567 31. Seto AH, Abu-Fadel MS, Sparling JM, Zacharias SJ, Daly TS, Harrison AT, et al.
21 568 Real-time ultrasound guidance facilitates femoral arterial access and reduces vascular
22 569 complications: FAUST (Femoral Arterial Access with Ultrasound Trial). *JACC*
23 570 *Cardiovasc Interv*. 2010;
24 571 32. Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation*. 2011;
25 572 33. Kern MJ. *Interventional Cardiac Catheterization Handbook*. Interv Card Catheter
26 573 *Handb*. 1977;
27 574 34. Tavris DR, Wang Y, Jacobs S, Gallauresi B, Curtis J, Messenger J, et al. Bleeding and
28 575 vascular complications at the femoral access site following percutaneous coronary
29 576 intervention (PCI): An evaluation of hemostasis strategies. *J Invasive Cardiol*. 2012;
30 577 35. Bernat I, Horak D, Stasek J, Mates M, Pesek J, Ostadal P, et al. ST-segment elevation
31 578 myocardial infarction treated by radial or femoral approach in a multicenter
32 579 randomized clinical trial: The STEMI-RADIAL trial. *J Am Coll Cardiol*. 2014;
33 580 36. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, et al.
34 581 Radial versus femoral randomized investigation in st-segment elevation acute coronary
35 582 syndrome: The rifle-steacs (radial versus femoral randomized investigation in st-
36 583 elevation acute coronary syndrome) study. *J Am Coll Cardiol*. 2012;
37 584 37. Diehl D, de Ribamar Costa J, Costa R, de Mello BG, Chamié D, Jatene T, et al.
38 585 PROPENSITY-SCORE COMPARISON OF PATIENTS WITH STABLE
39 586 CORONARY ARTERY DISEASE UNDERGOING PERCUTANEOUS
40 587 CORONARY INTERVENTION BY RADIAL VERSUS FEMORAL APPROACH. *J*
41 588 *Am Coll Cardiol*. 2016;
42 589 38. Rao S V., Hess CN, Barham B, Aberle LH, Anstrom KJ, Patel TB, et al. A registry-
43 590 based randomized trial comparing radial and femoral approaches in women undergoing
44 591 percutaneous coronary intervention: The SAFE-PCI for women (study of access site
45 592 for enhancement of PCI for women) trial. *JACC Cardiovasc Interv*. 2014;
46 593 39. Koifman E, Gaglia MA, Escarcega RO, Bernardo NL, Lager RA, Gallino RA, et al.
47 594 Comparison of transradial and transfemoral access in patients undergoing percutaneous
48 595 coronary intervention for complex coronary lesions. *Catheter Cardiovasc Interv*. 2017;
49 596 40. Alaswad K, Menon R V., Christopoulos G, Lombardi WL, Karpaliotis D, Grantham
50 597 JA, et al. Transradial approach for coronary chronic total occlusion interventions:
51 598 Insights from a contemporary multicenter registry. *Catheter Cardiovasc Interv*. 2015;
52 599 41. Watt J, Austin D, Mackay D, Nolan J, Oldroyd KG. Radial Versus Femoral Access for

- 1
2
3 600 Rotational Atherectomy: A UK Observational Study of 8622 Patients. *Circ Cardiovasc*
4 601 *Interv.* 2017;
5 602 42. Doyle BJ, Ting HH, Bell MR, Lennon RJ, Mathew V, Singh M, et al. Major Femoral
6 603 Bleeding Complications After Percutaneous Coronary Intervention. Incidence,
7 604 Predictors, and Impact on Long-Term Survival Among 17,901 Patients Treated at the
8 605 Mayo Clinic From 1994 to 2005. *JACC Cardiovasc Interv.* 2008;
9 606 43. Goel PK, Jatain S, Khanna R, Pandey CM. Left main PCI: An observational analysis
10 607 from large single-centre experience. *Indian Heart J.* 2016;
11 608 44. Gorol J, Tajstra M, Hudzik B, Lekston A, Gąsior M. Comparison of outcomes in
12 609 patients undergoing rotational atherectomy after unsuccessful coronary angioplasty
13 610 versus elective rotational atherectomy. *Postep w Kardiologii Interwencyjnej.* 2018;
14 611 45. Kinnaird T, Anderson R, Ossei-Gerning N, Gallagher S, Large A, Strange J, et al.
15 612 Vascular Access Site and Outcomes Among 26,807 Chronic Total Coronary Occlusion
16 613 Angioplasty Cases From the British Cardiovascular Interventions Society National
17 614 Database. *JACC Cardiovasc Interv.* 2017;
18 615 46. Maeremans J, Palmers PJ, Dens J. Initial experience and feasibility of the new low-
19 616 profile stingray catheter as part of the antegrade dissection and re-entry
20 617 revascularization strategy for coronary chronic total occlusions. *Am J Case Rep.* 2017;
21 618 47. Kinnaird T, Cockburn J, Gallagher S, Choudhury A, Sirker A, Ludman P, et al.
22 619 Temporal changes in radial access use, associates and outcomes in patients undergoing
23 620 PCI using rotational atherectomy between 2007 and 2014: results from the British
24 621 Cardiovascular Intervention Society national database. *Am Heart J.* 2018;
25 622 48. Yin WH, Tseng CK, Tsao TP, Jen HL, Huang WP, Huang CL, et al. Transradial versus
26 623 transfemoral rotablation for heavily calcified coronary lesions in contemporary drug-
27 624 eluting stent era. *J Geriatr Cardiol.* 2015;
28 625 49. Yang YJ, Kandzari DE, Gao Z, Xu B, Chen JL, Qiao S Bin, et al. Transradial versus
29 626 transfemoral method of percutaneous coronary revascularization for unprotected left
30 627 main coronary artery disease: Comparison of procedural and late-term outcomes.
31 628 *JACC Cardiovasc Interv.* 2010;
32 629 50. Kinnaird T, Anderson R, Gallagher S, Sirker A, Ludman P, de Belder M, et al. Access
33 630 Site and Outcomes for Unprotected Left Main Stem Percutaneous Coronary
34 631 Intervention: An Analysis of the British Cardiovascular Intervention Society Database.
35 632 *JACC Cardiovasc Interv.* 2018;
36 633 51. Ziakas A, Klinke P, Mildenerger R, Fretz E, Williams MB, Della Siega A, et al.
37 634 Comparison of the Radial and Femoral Approaches in Left Main PCI: A Retrospective
38 635 Study. *J Invasive Cardiol.* 2004;
39 636 52. Gao Z, Xu B, Yang Y, Kandzari DE, Sun Z, Qiao S, et al. Transradial versus
40 637 transfemoral method of two-stent implantation for true bifurcation lesions: Comparison
41 638 of immediate and long-term outcomes. *J Interv Cardiol.* 2014;
42 639 53. Hsueh SK, Hsieh YK, Wu CJ, Fang CY, Youssef AA, Chen CJ, et al. Immediate
43 640 results of percutaneous coronary intervention for unprotected left main coronary artery
44 641 stenoses: Transradial versus transfemoral approach. *Chang Gung Med J.* 2008;
45 642 54. Chung S, Yang JH, Choi SH, Song Y Bin, Hahn JY, Choi JH, et al. Transradial versus
46 643 transfemoral intervention for the treatment of left main coronary bifurcations: Results
47 644 from the COBIS (COronary Bifurcation Stenting) II registry. *J Invasive Cardiol.* 2015;
48 645 55. Williams PD, Eichhöfer J, Mamas MA, Arnous S, Fath-Ordoubadi F, Fraser D.
49 646 Transradial intervention via large-bore guide catheters: A study of coronary bifurcation
50 647 disease treatment using the crush technique. *J Invasive Cardiol.* 2013;
51 648 56. Bernat I, Aminian A, Pancholy S, Mamas M, Gaudino M, Nolan J, et al. Best Practices
52 649 for the Prevention of Radial Artery Occlusion After Transradial Diagnostic
53
54
55
56
57
58
59
60

- 1
2
3 650 Angiography and Intervention: An International Consensus Paper. JACC:
4 651 Cardiovascular Interventions. 2019.
- 5 652 57. Saito S, Ikei H, Hosokawa G, Tanaka S. Influence of the ratio between radial artery
6 653 inner diameter and sheath outer diameter on radial artery flow after transradial
7 654 coronary intervention. *Catheter Cardiovasc Interv.* 1999;
- 8 655 58. Kotowycz MA, Džavík V. Radial artery patency after transradial catheterization. *Circ*
9 656 *Cardiovasc Interv.* 2012;
- 10 657 59. Rademakers LM, Laarman GJ. Critical hand ischaemia after transradial cardiac
11 658 catheterisation: An uncommon complication of a common procedure. *Netherlands Hear*
12 659 *J.* 2012;
- 13 660 60. Ayan M, Smer A, Azzouz M, Abuzaid A, Mooss A. Hand ischemia after transradial
14 661 coronary angiography: Resulting in right ring finger amputation. *Cardiovasc*
15 662 *Revascularization Med.* 2015;
- 16 663 61. Amin H. Prevention of radial artery occlusion: It's the right thing to do.
17 664 *EuroIntervention.* 2015;
- 18 665 62. Kiemeneij F, Yoshimachi F, Matsukage T, Amoroso G, Fraser D, Claessen BE, et al.
19 666 Focus on maximal miniaturisation of transradial coronary access materials and
20 667 techniques by the Slender Club Japan and Europe: An overview and classification.
21 668 *EuroIntervention.* 2015.
- 22 669 63. Mamas MA, Fath-Ordoubadi F, Fraser DG. Atraumatic complex transradial
23 670 intervention using large bore sheathless guide catheter. *Catheter Cardiovasc Interv.*
24 671 2008;
- 25 672 64. Fraser D, Mamas MA. Transradial Sheathless Approach for PCI. *Current Cardiology*
26 673 *Reports.* 2015.
- 27 674 65. Horie K, Tada N, Isawa T, Matsumoto T, Taguri M, Kato S, et al. A randomised
28 675 comparison of incidence of radial artery occlusion and symptomatic radial artery spasm
29 676 associated with elective transradial coronary intervention using 6.5 Fr SheathLess
30 677 Eaucath Guiding Catheter vs. 6.0 Fr Glidesheath Slender. In: *EuroIntervention.* 2018.
- 31 678 66. Mohsen A, Alqasrawi M, Shantha GPS, DeZorzi C, Panaich S. Comparison of Radial
32 679 Artery Occlusion Following Transradial Access for Percutaneous Coronary
33 680 Intervention Using Sheath-based versus Sheathless Technique. *Sci Rep.* 2018;
- 34 681 67. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis
35 682 in myocardial infarction (TIMI) trial, phase I: A comparison between intravenous
36 683 tissue plasminogen activator and intravenous streptokinase. Clinical findings through
37 684 hospital discharge. *Circulation.* 1987;
- 38 685 68. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute
39 686 Myocardial Infarction. *N Engl J Med.* 1993;
- 40 687 69. White HD, Aylward PE, Gallo R, Bode C, Steg G, Steinhubl SR, et al. Hematomas of
41 688 at least 5 cm and outcomes in patients undergoing elective percutaneous coronary
42 689 intervention: Insights from the SafeTy and Efficacy of Enoxaparin in PCI patients, an
43 690 international randomized Evaluation (STEEPLE) trial. *Am Heart J.* 2010;
- 44 691 70. van Leeuwen MAH, Hollander MR, van der Heijden DJ, van de Ven PM, Opmeer
45 692 KHM, Taverne YJHJ, et al. The ACRA Anatomy Study (Assessment of Disability
46 693 After Coronary Procedures Using Radial Access): A Comprehensive Anatomic and
47 694 Functional Assessment of the Vasculature of the Hand and Relation to Outcome After
48 695 Transradial Catheterization. *Circ Cardiovasc Interv.* 2017;
- 49 696 71. Ul Haq MA, Rashid M, Kwok CS, Wong CW, Nolan J, Mamas MA. Hand dysfunction
50 697 after transradial artery catheterization for coronary procedures. *World J Cardiol.* 2017;
- 51 698 72. Ijsselmuiden A, Zwaan E, Kofflard M, Holtzer C. TCT-639 Upper extremity function
52 699 after transradial PCI: preliminary long term results of the ARCUS trial. *J Am Coll*

1
2
3 700 Cardiol. 2017;
4 701 73. Zwaan EM, Koopman AGMM, Holtzer CAJ, Zijlstra F, Ritt MJPF, Amoroso G, et al.
5 702 Revealing the impact of local access-site complications and upper extremity
6 703 dysfunction post transradial percutaneous coronary procedures. Netherlands Heart
7 704 Journal. 2015.
8 705
9 706

10 706
11 707 **Figure legend**
12 708

13 709 Figure 1: Inclusion flowchart for the COLOR trial.

14 710 **Caption:** *Graphic representation of inclusion for the COLOR trial. STEMI = ST elevation*
15 711 *myocardial infarction, BARC = Bleeding Academic Research Group, MACE = Major*
16 712 *Adverse Cardiovascular Events.*
17 713

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

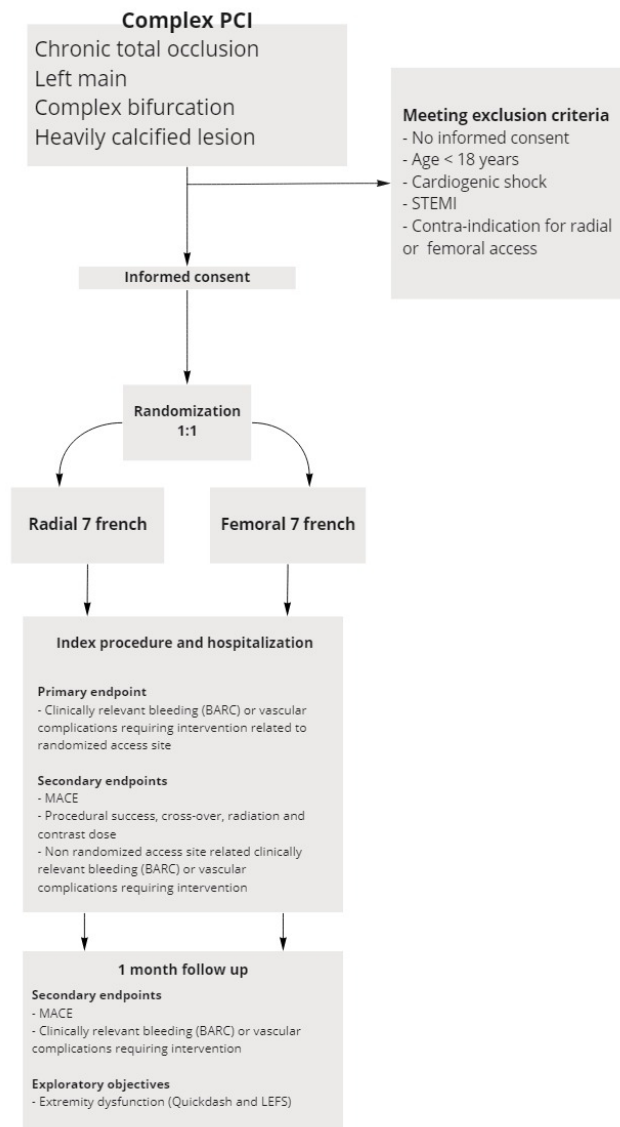


Figure 1: enrollment flowchart of the COLOR trial

300x413mm (72 x 72 DPI)

Supplementary file I: CEC manual for adjudicating bleeding and vascular complications

Classification and Definition

Bleeding

BARC 0

No bleeding or hematoma.

BARC 1

Every bleeding or hematoma not meeting the criteria for BARC 2 or higher.

BARC 2

Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, (prolonged) hospitalization, or treatment by a health care professional.

Specified for radial access and femoral access in this appendix

BARC 3a

Overt bleeding + Hb drop of 3-5 g/dl (1.9 – 3.1 mmol/L), or any transfusion with overt bleeding (independent of Hb)

BARC 3b

Overt bleeding + Hb drop >5g/dl (>3.1 mmol/L), or cardiac tamponade, or bleeding requiring surgical intervention and/or IV vasoactive agents

BARC 3c

Intracranial hemorrhage or intraocular bleedings

BARC 4

CABG related bleeding

BARC 5

Fatal bleeding

Vascular complications

Retroperitoneal hematoma, (pseudo) aneurysm, infection and arteriovenous-fistula or vascular occlusion requiring intervention. Specified for radial access and femoral access in this appendix

Radial access

Specification of BARC 2 bleedings

1. Prolonged hospitalization

Any bleeding that leads to one or more extra hospitalization day(s)

- Based on standard discharge policy of hospital

- For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

2. Additional compression therapy

Any additional compression therapy after successful primary hemostasis

- Bleeding after removal of first TR band and additional compression bandage or TR band is needed

- Ongoing bleeding with first TR band and additional compression therapy is needed

- Adding 1 or 2cc of air in the first TR band due to slight oozing should not be scored as BARC 2

3. Additional investigations

Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

4. Additional therapy

- Any additional or change of therapy related to bleeding/hematoma
- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation of medical therapy (i.e. vitamin K, hematological products)
 - Percutaneous intervention (i.e. coiling)

Specification of vascular complications

- Vascular complications requiring intervention: percutaneous, surgical, medical
- (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
 - Infection (i.e. antibiotics)
 - Arteriovenous-fistula (i.e. percutaneous or surgical intervention)
 - Radial artery occlusion (percutaneous intervention, heparin therapy)
 - Dissection (i.e. percutaneous or surgical intervention)
 - Compartment syndrome (i.e. percutaneous or surgical intervention)

Femoral access

Specification BARC 2 bleeding

1. Prolonged hospitalization

- Any bleeding that leads to one or more extra hospitalization day(s)
- Based on standard discharge policy of hospital
 - For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

2. Additional compression therapy

- Any additional compression therapy after successful primary hemostasis:
- New compression therapy after removal of the first bandage, or additional compression after closure device
 - Prolonging compression bandage due to slight oozing should not be scored BARC 2, when this will not lead to prolonged hospitalization (one or more days).

3. Additional investigations

- Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, angiography or CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

4. Additional therapy

- Any additional or change of therapy related to bleeding/hematoma
- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation medical therapy (i.e. vitamin K, hematological products)
 - Percutaneous intervention (i.e. coiling or stenting of peripheral arteries)

Specification of vascular complications

- 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)

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
- 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)

For peer review only

Supplementary file II

Participation Information Sheet and Consent Form

Centre Number: _____ Patient Number: _____

Study Title: COLOR study - Comparative study of complex Percutaneous Coronary Intervention (PCI) procedures with large catheters through the radial artery or femoral artery.

Principle Investigator: Site specific

Name and Address: Site specific

Telephone: Site specific

Sponsor: ISALA Heart Centre, Zwolle, Netherlands.

1. Introduction

We would like to invite you to take part in this study. Participation is voluntary. If you would like to participate, we need your written consent. Before you decide whether to participate in the study or not, you should know what the study entails. Read this information carefully and ask the researcher for an explanation if you have any questions. If you would like more information, you can also consult the independent expert listed at the end of this letter. You can also discuss it with your partner, friends or family.

2. General information

This study was initiated by the cardiology partnership of the Isala hospital in

1
2
3 Zwolle, and is being conducted by multiple cardiologists in the Netherlands,
4 Belgium, Germany, Switzerland and England. The study requires 388 subjects
5 from different countries.
6

7
8 All research is looked at by an independent group of people called Research Ethics
9 Committee to protect your safety, rights, wellbeing and dignity. This study has been
10 reviewed and given favorable opinion by the local Ethics Committee.
11
12

13 14 **3. Background of the study**

15
16 The radial artery (artery in the arm) is smaller than the femoral artery (artery in the leg).
17 Cardiac catheterization and PCI are already often performed through the radial artery. If
18 the PCI procedure required a thicker catheter because the cardiologist needed more
19 sturdiness to complete it, the groin was often used as the access site due to the larger
20 artery. With the development of a thin-walled radial artery sheath, complex PCI
21 procedures with thicker catheters can now also be performed through the radial artery. A
22 complex PCI procedure through the radial artery may lead to fewer access-site
23 complications than through the femoral artery, while providing a similar PCI result, but
24 this has not yet been properly researched.
25
26
27
28
29
30
31

32 **4. What your participation will entail**

33
34 If you wish to participate, we will first check whether both the groin and the wrist can
35 be used for the PCI procedure.
36

37
38 Before the procedure, we will ask you questions regarding whether or not you can use
39 your arms and legs properly. We will ask you the same questions again one month
40 after the procedure. You will also be asked to complete 2 questionnaires.
41

42
43 If both the radial and femoral arteries can be used, we will randomly assign you,
44 - to determine whether you will be treated through the wrist or the groin.
45

46
47 If you are selected for the wrist procedure, we will use the modern sheath. If you are
48 selected for the groin procedure, we will use the standard sheath.
49

50
51 Aside from the potential difference in sheath, the treatment you will receive will be
52 exactly the same as if you did not participate in the study. The procedure may
53 sometimes require the use of a 2nd catheter. In that case, the cardiologist will
54 determine where the access site for the second catheter will be.
55
56

57
58 The examinations you receive before and after the treatment are also exactly the same
59 as if you did not participate in the study. Those examinations include an
60 electrocardiography (ECG), a blood test and an inspection of the access site (groin or
wrist).

1
2
3
4 The study will require the collection of your medical records for up to one month after
5 the procedure.
6
7

8 **5. What is expected of you?**

9 For a good outcome of the study, it is important that you answer the questions during
10 the study visit and the 1-month check-up to the best of your knowledge.
11
12

13 **6. Possible complications and other/adverse effects/complaints**

14
15 In general, the procedure is performed using standard methods and participation in
16 this study will not result in additional adverse effects. The materials used (including the
17 sheaths) have been approved and are already in use for complex PCI procedures for
18 patients who are not participating in a study. The only inconvenience you may
19 experience is that we will contact you after one month to ask you some questions.
20 Trans-Femoral and Trans-radial access will be performed according to the local protocol
21 with the direct needle technique or venous cannula technique. The complications are
22 the same as standard of care procedure and will be fully covered by the
23 Doctor/Investigator during the discussion before consenting to the procedure.
24 Complications that may arise from inserting and removing a sheath are:
25
26

- 27 -Bleeding
- 28 -Vascular problems
- 29 -Blood vessel closure
- 30
- 31
- 32
- 33
- 34
- 35

36 **7. Possible advantages and disadvantages**

37
38 Before you decide to participate in the study, it is important to consider the possible
39 advantages and disadvantages.
40
41

42 If you participate in the study, there is a chance that you will receive exactly the same
43 treatment as if you were not participating. If you are selected for the treatment group
44 with the modern sheath through the wrist, you may have a reduced chance of
45 accesssite complications, but this has not yet been proven. PCI performed through the
46 femoral artery can also result in a longer hospital stay.
47
48
49
50

51 **8. If you do not wish to participate or wish to end participation in the study**

52 You decide whether or not to participate in the study. Participation is voluntary.
53
54

55 If you do not wish to participate, the PCI procedure with the thicker catheter will be
56 performed in the usual manner. This can be done through the groin or the wrist.
57
58

59 If you do participate, you can change your mind and withdraw at any time, even during
60 the study. You will then receive the standard treatment again. You do not have to
provide a reason for stopping. If the procedure has already begun, it cannot be

1
2
3 reversed and you will also require a follow-up check-up. The data collected up to the
4 moment of withdrawal will be used for the study.
5

6 7 **9. End of the study**

8
9 Your participation in the study ends when:

- 11 You have had the check-up one month after the procedure;
- 12 You choose to stop;

13
14 The researcher feels it is better for you to stop;

15
16 The Isala cardiology partnership, the government or the supervising medical.

17
18 The entire study is complete when all participants are finished.
19

20 21 22 **10. Use and storage of your records**

23
24 All of your records will remain confidential. To protect your privacy, your records will be
25 given a code. Your name and other information which directly identifies you will be
26 omitted. The records can only be traced back to you with the key to the code. Only the
27 study doctor and research staff know which code you have. The study will only ever
28 use your data with that code, never with your name. The key to the code will remain in
29 possession of the study team. Reports on the study will also only use that code.
30
31

32
33
34 Some people will be allowed to access your medical and personal information. Access to
35 your medical and personal Information will be by the study Doctor/Investigator and the
36 research team at site. The Sponsor, representatives of the Sponsor (including the
37 Contract Research Organisation, study monitors, auditors and project manager. Ethics
38 committee and government agencies where permitted or required by law. This is
39 necessary to confirm that the study has been conducted properly and reliably. - They will
40 keep your information confidential. By signing the consent form, you agree to the
41 collection, storage and viewing of your medical and personal records.
42
43
44
45
46
47
48
49
50

51 **11. More information on your rights with regard to data processing**

52
53 All the information that is collected during the study is kept confidential and there are
54 strict laws in place which safeguard the privacy of the patient at every stage. We will
55 be using your information (samples and medical records) in order to undertake this
56 study and we will act as the data controller for this study. This means that we are
57 responsible for looking after your information and using it properly. Your identity and
58 contact details will be confidential and all the data collected will be anonymized so you
59 cannot be
60

1
2
3 identified.

4
5 A description of this study will be available on <http://www.ClinicalTrials.gov>, and this
6 web site will not include information that can identify you.

7 ISALA Heart Centre, Zwolle, is the Sponsor for this study based in the Netherlands.
8 We will be using information from your medical records in order to undertake this
9 study and will act as the data controller for this study. This means that we are for
10 looking after your information and using it properly. ISALA Heart Centre will keep
11 identifiable information about you for 15 years after the study has finished. Your
12 rights to access, change or move your information are limited, as we need to
13 manage your information in specific ways in order for the research to be reliable and
14 accurate. If you withdraw from the study, we will keep the information about you
15 that we have already obtained. To safeguard your rights, we will use the minimum
16 personally identifiable information possible.
17
18
19
20
21
22

23 The local site will keep your name, ID number and contact details confidential and
24 will not pass this information to ISALA Heart Centre. The local site will use this
25 information as needed, to contact you about the research study, and make sure that
26 relevant information about the study is recorded for you care, and to oversee the
27 quality of the study. Certain individuals from ISALA Heart Centre and regulatory
28 organisations may look at your medical and research records to check the accuracy
29 or the research study. ISALA Heart Centre will only receive information without any
30 identifying information. The people who analyse the information will not be able to
31 identify you and will not be able to find out your name, NHS number or contact
32 details.
33
34
35
36
37

38 **12. Insurance for subjects**

39
40 If you participate in the study you will face the same risks as for the standard
41 treatment of your condition. The study is insured with HDI Global SE – UK Policy
42 Number 390-08414363 and has a liability insurance for £5 million.
43
44
45
46

47 **13. Informing your GP**

48
49 We will always notify your GP and/or treating specialist that you are participating in the
50 study. This is for your own safety. If you do not agree to this, you cannot participate in
51 the study. In the event of complications, we may contact your doctor or GP for
52 information such as your medical history or use of medicines.
53
54
55

56 **15. Questions**

57
58 If you have any questions or concerns, please contact the study doctor or the
59 research team.
60

1
2
3 If you have any complaints or require general advice you can contact the hospital's
4 Patient Advice and Liaison Service (PALS).
5

6 **16. Signing the consent form**

7
8
9 Once you have had sufficient time to think about it, you will be asked to decide
10 whether or not to participate in this study. If you consent, we will ask you to confirm
11 your consent in writing on the appropriate consent form. By giving your written
12 consent, you acknowledge that you have understood the information and agree to
13 participation in
14 the study.
15
16

17
18 The signature sheet will be kept by the researcher. You will receive a duplicate or a
19 second copy of the consent form.
20

21
22 Thank you for your reading this information sheet.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Consent form

COLOR trial

- I have read the information letter. I was given the opportunity to ask questions. My questions have been answered to my satisfaction. I have had enough time to decide whether or not to participate. I am aware that participation is voluntary.
- I am also aware that I can decide not to participate or to withdraw from the study at any time. I need not give a reason for this.
- I consent to informing my GP that I am participating in this study.
- I am aware that some people have access to my records. Those people are listed in this information letter.
- I consent to the collection and use of my information in the manner and for the purposes listed in the information letter.
- I consent to the storage of my information at the research site for 15 years after this study.
- I wish to participate in this study.

Name of participant:

Signature:

Date : __ / __ / __

Name of investigator:

Signature:

Date : __ / __ / __



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P
	2b	All items from the World Health Organization Trial Registration Data Set	P 3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	P 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P 1
	5b	Name and contact information for the trial sponsor	P 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P 4
	6b	Explanation for choice of comparators	P 4
Objectives	7	Specific objectives or hypotheses	P 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P 4

Methods: Participants, interventions, and outcomes

1				
2				
3				
4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P 4
5				
6				
7				
8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P 5
9				
10				
11				
12				
13	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 6
14				
15				
16		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
17				
18				
19				
20				
21		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
22				
23				
24				
25		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
26				
27				
28	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P 5
29				
30				
31				
32				
33				
34				
35				
36	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 1
37				
38				
39				
40				
41	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P 6
42				
43				
44				
45	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P 6
46				
47				

Methods: Assignment of interventions (for controlled trials)

Allocation:

51				
52				
53	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P 6
54				
55				
56				
57				
58				
59				
60				

1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	N/A
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	N/A
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	N/A
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13		17b	If blinded, circumstances under which unblinding is permissible, and	N/A
14			procedure for revealing a participant's allocated intervention during	
15			the trial	
16				
17				
18				
19				
20	Methods: Data collection, management, and analysis			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	P 11-12
22	methods		trial data, including any related processes to promote data quality (eg,	
23			duplicate measurements, training of assessors) and a description of	
24			study instruments (eg, questionnaires, laboratory tests) along with	
25			their reliability and validity, if known. Reference to where data	
26			collection forms can be found, if not in the protocol	
27		18b	Plans to promote participant retention and complete follow-up,	P 6
28			including list of any outcome data to be collected for participants who	
29			discontinue or deviate from intervention protocols	
30	Data	19	Plans for data entry, coding, security, and storage, including any	P 6
31	management		related processes to promote data quality (eg, double data entry;	
32			range checks for data values). Reference to where details of data	
33			management procedures can be found, if not in the protocol	
34	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	P 6
35	methods		Reference to where other details of the statistical analysis plan can be	
36			found, if not in the protocol	
37		20b	Methods for any additional analyses (eg, subgroup and adjusted	P 6
38			analyses)	
39		20c	Definition of analysis population relating to protocol non-adherence	N/A
40			(eg, as randomised analysis), and any statistical methods to handle	
41			missing data (eg, multiple imputation)	
42				
43				
44				
45				
46				
47				
48				
49				
50				
51				
52	Methods: Monitoring			
53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	N/A
54			and reporting structure; statement of whether it is independent from	
55			the sponsor and competing interests; and reference to where further	
56			details about its charter can be found, if not in the protocol.	
57			Alternatively, an explanation of why a DMC is not needed	
58				
59				
60				

1				
2		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
3				
4				
5				
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P 4
7				
8				
9				
10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
12				
13				
14				
15	Ethics and dissemination			
16				
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P 7
18				
19				
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P 7-8
21				
22				
23				
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P 7
27				
28				
29		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
30				
31				
32	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P 7
33				
34				
35				
36				
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P 1
38				
39				
40	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
41				
42				
43				
44	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
45				
46				
47				
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P 7
49				
50				
51				
52				
53		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
54				
55				
56				
57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
58				
59				
60				

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp II
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

For peer review only

BMJ Open

Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR trial study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038042.R2
Article Type:	Protocol
Date Submitted by the Author:	03-Jun-2020
Complete List of Authors:	Meijers, Thomas; Isala Hospitals, Cardiology Aminian, Adel ; Centre Hospitalier Universitaire de Charleroi, Cardiology Teeuwen, Koen; Catharina Hospital, Cardiology van Wely, Marleen; Radboudumc, Cardiology Schmitz, Thomas; Elisabeth-Krankenhaus-Essen GmbH, Cardiology Dirksen, Maurits; Noordwest Ziekenhuisgroep, Cardiology van der Schaaf, Rene; OLVG, Cardiology Iglesias, Juan; Geneva University Hospitals, Cardiology Agostoni, Pierfrancesco; ZNA, Cardiology Dens, Joseph; Ziekenhuis Oost-Limburg, Cardiology Knaapen, Paul; Amsterdam UMC - Locatie VUMC, Cardiology Rathore, Sudhir; Frimley Health NHS Foundation Trust, Cardiology Ottervanger, Jan Paul; Isala Hospitals, Cardiology Dambrink, Jan-Henk; Isala Hospitals, Cardiology Roolvink, Vincent; Isala Hospitals, Cardiology Gosselink, Marcel; Isala Hospitals, Cardiology Hermanides, Renicus; Isala Hospitals, Cardiology van Royen, Niels; Radboudumc, Cardiology van Leeuwen, Maarten; Isala Hospitals, Cardiology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	Coronary intervention < CARDIOLOGY, CARDIOLOGY, Coronary heart disease < CARDIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1
5 2 Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR
6 3 trial study protocol
7 4
8 5

9 6 Thomas A. Meijers MD^{a*}, Adel Aminian MD^{b*}, Koen Teeuwen MD, PhD^c, Marleen van
10 7 Wely MD^d, Thomas Schmitz MD, PhD^e, Maurits T. Dirksen MD, PhD^f, René J. van der
11 8 Schaaf MD, PhD^g, Juan F. Iglesias MD, PhD^h, Pierfrancesco Agostoni MD, PhDⁱ, Joseph
12 9 Dens MD, PhD^j, Paul Knaapen MD, PhD^k, Sudhir Rathore MD, FRCP^l, Jan Paul Ottervanger
13 10 MD, PhD^a, Jan Henk E. Dambrink MD, PhD^a Vincent Roolvink MD, PhD^a, A.T. Marcel
14 11 Gosselink MD, PhD^a, Renicus S. Hermanides MD, PhD^a, Niels van Royen MD, PhD^d,
15 12 Maarten A.H. van Leeuwen MD, PhD^a

16 13
17 14
18 14 * Both authors contributed equally.
19 15

20 16 Word count: 3758
21 17

22 18 Departments and institutions

23 19 ^a Department of Cardiology, Isala Heart Center, Zwolle, the Netherlands

24 20 ^b Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi,
25 21 Belgium

26 22 ^c Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands

27 23 ^d Department of Cardiology, Radboud University Medical Center, Nijmegen, the
28 24 Netherlands

29 25 ^e Department of Cardiology, Elisabeth Krankenhaus, Essen, Germany

30 26 ^f Department of Cardiology, Northwest Clinics, Alkmaar, the Netherlands

31 27 ^g Department of Cardiology, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the
32 28 Netherlands

33 29 ^h Department of Cardiology, Geneva University Hospital, Geneva, Switzerland

34 30 ⁱ Department of Cardiology, ZNA Middelheim, Antwerp, the Netherlands

35 31 ^j Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium

36 32 ^k Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands

37 33 ^l Department of Cardiology, Frimley Health NHS Foundation Trust, Surrey, United
38 34 Kingdom
39 35

40 36 Sources of funding

41 37 Terumo EMEA (Leuven, Belgium) supported this investigator-initiated study by an
42 38 unrestricted grant.
43 39

44 40 Conflict of interest

45 41 Maarten A.H. van Leeuwen, Adel Aminian and and Juan F. Iglesias are consultants for
46 42 Terumo corp., Juan F. Iglesias and Thomas Schmitz have received honoraria/speakers fee for
47 43 Terumo corp., the other authors have no conflicts of interest to declare.
48 44

49 45 Clinical trial registration

50 46 ClinicalTrials.gov identifier: NCT03846752.
51 47

52 48 Address for correspondence

53 49 dr. M.A.H. van Leeuwen, Isala Heart Center, Dr. van Heesweg 2, 8025 AB Zwolle, The
54 50 Netherlands. Email: m.a.h.van.leeuwen@isala.nl
55 51
56 52
57 53
58 54
59 55
60 56

Abstract**Introduction**

The radial artery has become the standard access site for percutaneous coronary intervention (PCI) in stable coronary artery disease and acute coronary syndrome, because of less access site related bleeding complications. Patients with complex coronary lesions are underrepresented in randomized trials comparing radial with femoral access with regard to safety and efficacy. The femoral artery is currently the most applied access site in patients with complex coronary lesions, especially when large bore guiding catheters are required. With slender technology, transradial PCI may be increasingly applied in patients with complex coronary lesions when large bore guiding catheters are mandatory and might be a safer alternative as compared to the transfemoral approach.

Methods and analysis

A total of 388 patients undergoing complex PCI will be randomized to radial 7 French access with Terumo Glidesheath Slender (Terumo Corp., Japan) or femoral 7 French access as comparator. The primary outcome is the incidence of the composite end-point of clinically relevant access site related bleeding and/or vascular complications requiring intervention. Procedural success and major adverse cardiovascular events up to 1 month will also be compared between both groups.

Ethics and dissemination

Ethical approval for the study was granted by the local Ethics Committee at each recruiting center ('Medisch Ethische Toetsing Commissie Isala Zwolle', 'Commissie voor medische ethiek ZNA', 'Comité Medische Ethiek Ziekenhuis Oost-Limburg', 'Comité d'éthique CHU-Charleroi – ISPPC', 'Commission cantonale d'éthique de la recherche CCER – République et Canton de Genève', 'Ethik Kommission de Ärztekammer Nordrhein' and 'Riverside Research Ethics Committee'). The trial outcomes will be published in peer-reviewed journals of the concerned literature. The COLOR trial has been administered in the ClinicalTrials.gov database, reference number: NCT03846752.

Strengths and limitations of this study

- The design as a randomized 1:1 open label study (radial 7 Fr versus femoral 7) and the vast experience with complex PCI of the participating centers
- Clinical Event Committee adjudicated and clinically relevant primary endpoint
- First study assessing extremity dysfunction after complex large bore PCI
- As a limitation, bias could be derived from the unblinded nature of the study for the treating interventional cardiologist
- As a limitation, use of secondary access sites for hybrid approach of CTO lesions will influence efficacy outcomes, although it will not influence the primary endpoint.

Keywords

Complex percutaneous coronary intervention - Chronic total occlusion - Radial access - Femoral access - Slender

Abbreviations

PCI = percutaneous coronary intervention

CTO = chronic total occlusion

CABG = coronary artery bypass grafting

ACS = acute coronary syndrome

BARC = bleeding academic research consortium

1
2
3 101 MACE = major adverse cardiovascular events
4 102 AE = adverse event
5 103 SAE = serious adverse event
6 104 TR= transradial
7 105 TRA= transradial access
8 106 TF = transfemoral
9 107 TFA = transfemoral access
10 108 Fr = French
11
12 109
13 110
14 111
15 112
16 113
17 114
18 115
19 116
20 117
21 118
22 119
23 120
24 121
25 122
26 123
27 124
28 125
29 126
30 127
31 128
32 129
33 130
34 131
35 132
36 133
37 134
38 135
39 136
40 137
41 138
42 139
43 140
44 141
45 142
46 143
47 144
48 145
49 146
50 147
51 148
52 149
53 150
54
55
56
57
58
59
60

For peer review only

151 **Background**

152 The radial artery has become the standard access site for percutaneous coronary interventions
153 (PCI), driven not only by lower rates of major bleeding and vascular complications, but also
154 by reduced mortality in patients presenting with acute coronary syndrome (ACS) (1–3). This
155 has led the 2018 ESC/EACTS Guidelines on myocardial revascularization to recommend
156 transradial access (TRA) over transfemoral access (TFA) as a class Ia indication in ACS
157 patients undergoing invasive management (4). In patients with stable coronary artery disease,
158 several small randomized trials comparing radial and femoral access have shown significantly
159 less bleeding in favor of radial access but no mortality benefit (5–7). Of note, patients with
160 complex coronary lesions were not included in these trials or not specifically described. PCI
161 of chronic total occlusions (CTO), left main disease, heavily calcified or complex bifurcation
162 lesions often require the use of large-bore guiding catheters (7 Fr or larger inner diameter).
163 Indeed, large-bore guiding catheters provide more back-up and stability in addition to better
164 materials' compatibility, leading to higher procedural success rates in more complex lesions
165 (8,9). Because of potential radial artery-sheath mismatch, spasms or back-up problems, the
166 femoral artery is still the most applied access site for complex PCI (10,11). In return, TFA
167 with increased sheath size is associated with bleeding and vascular complications and adverse
168 clinical outcome, including myocardial infarction (MI), stroke and death (12,13). The recent
169 availability of modern slender technology, such as the thin-walled radial introducer sheath
170 (Glidesheath Slender®, Terumo Corp., Japan), has the potential to expand the use of TRA for
171 complex PCI. As compared to the average outer diameter of a standard sheath, the outer
172 diameter of these slender sheaths has been reduced by approximately 1 Fr while maintaining
173 the inner-diameter equivalent. In a prospective single-arm study it was recently shown that
174 complex transradial (TR) PCI with a 7 Fr Glidesheath Slender is safe and effective (14).
175 Several observational studies have been published describing feasibility of large bore TRA for
176 PCI of CTO's, left main disease, heavily calcified lesions and complex bifurcations without
177 affecting procedural success rates (9,11,15–18). However, randomized data comparing TRA
178 and TFA for percutaneous treatment of complex coronary lesions are lacking. Therefore, we
179 have designed a randomized study, comparing the safety and efficacy of TRA and TFA for
180 complex PCI using large-bore guiding catheters.

181 **Methods**

182 *Study design*

183 The Complex Large-Bore Radial PCI (COLOR) trial is an investigator-initiated international
184 multi-center study with a prospective, randomized controlled design. Participating centers are
185 the Isala Heart Center (Zwolle, the Netherlands), Catharina Hospital (Eindhoven, the
186 Netherlands), Radboud University Medical Center (Nijmegen, The Netherlands), Elisabeth-
187 Krankenhaus (Essen, Germany), NorthWest Clinics (Alkmaar, the Netherlands), Onze Lieve
188 Vrouwe Gasthuis Hospital (Amsterdam, the Netherlands), Centre Hospitalier Universitaire de
189 Charleroi (Charleroi, Belgium), ZNA Middelheim (Antwerpen, Belgium), Hospital Oost-
190 Limburg (Genk, Belgium), Geneva University Hospital (Geneva, Switzerland), VU
191 University Medical Center (Amsterdam, The Netherlands) and Frimley NHS (Surrey, United
192 Kingdom). All centers have been selected based on their high volumes and experience with
193 complex PCI and large bore access. For CTO, each center has a dedicated program for an
194 average of 6 years, with 1-3 dedicated CTO operators and an average of 110 procedures per
195 year (spreading from 55 to 200 procedures per year). 83% of CTO procedures are done with
196 dual arterial access, with biradial access in 20%, bifemoral access in 24% and radial/femoral
197 (hybrid) access in the remaining 49% of cases. Large bore access is used in 89% of cases. For
198 non-CTO complex PCI, the participating centers have a dedicated program for an average of
199 11 years, performing an average of 245 procedures per year with 3-5 complex PCI operators.

201 76% of these cases are done with TRA and 24% with TFA. Large bore access is used in 62%
202 of all complex non CTO PCI.

203

204 *Trial organization*

205 The trial is approved by the appropriate ethics review board at each clinical site. Written
206 informed consent will be obtained from all patients before enrollment. The trial was designed
207 in accordance with the declaration of Helsinki. All data will be collected in an electronic data
208 capturing system, the eDREAM (electronic case record form Diagnostic REsearch And
209 Management). Diagram BV, Zwolle, the Netherlands will be responsible for overall trial and
210 data management, as well as monitoring of the study. Evaluation of serious adverse events is
211 being performed by an independent Data Safety Monitoring Board (DSMB). A Clinical
212 Events Committee (CEC) will review and adjudicate all end-point related adverse events. The
213 COLOR trial has been administered in the ClinicalTrials.gov database, reference number:
214 NCT03846752.

215

216 *Objectives*

217 The primary objective of this study is to investigate whether TR PCI is superior to
218 transfemoral (TF) PCI in complex coronary lesions with large-bore guiding catheters with
219 respect to clinically relevant access site related bleeding and/or vascular complications.

220

221 As secondary objectives, TR and TF large-bore access will be compared with regard to
222 procedural success, procedural time, fluoroscopy time, contrast use, crossover rates, major
223 adverse cardiovascular events (MACE) and non-access site related bleeding or vascular
224 complications for complex PCI.

225

226 For exploratory purposes extremity dysfunction and discomfort will be compared between TR
227 and TF treated patients for complex PCI with large-bore guiding catheters.

228

229 *Inclusion*

230 All patients of 18 years or older, presenting with stable coronary artery disease, unstable
231 angina or non-ST elevation myocardial infarction and planned for PCI of the following
232 complex coronary lesions: CTO, left main stem, heavily calcified lesions which may require
233 calcium modification techniques (rotational atherectomy or intravascular lithotripsy) and
234 complex bifurcations in whom the operator anticipates that a 7 Fr guiding catheter is
235 indicated, are screened for inclusion. CTO is defined as a lesion exhibiting TIMI 0-1 flow in a
236 native coronary artery with an occlusion duration of ≥ 3 months (19). Heavily calcified lesions
237 are characterized by multiple persisting opacifications of the coronary wall visible in more
238 than one projection surrounding the complete lumen of the coronary artery at the site of the
239 lesion (20). Complex bifurcation includes lesions with Medina classification 0.1.1, 1.1.1 or
240 1.0.1 (21). Patients with ST elevation myocardial infarction or cardiogenic shock will be
241 excluded. Patients with contraindications for femoral or radial access, such as occlusive
242 peripheral artery disease, known severe spasm or known anatomical variants prohibiting
243 radial or femoral access on both sides will be excluded as well. See also Figure 1 for graphic
244 representation of study inclusion.

245

246 *Randomization*

247 After providing written informed consent, eligible subjects are randomly assigned to receive
248 one of the two study treatments in a 1:1 ratio. Treatment assignments are performed centrally
249 through a dedicated website as part of the electronic Case Report Form (eCRF) according to a
250 computer-generated random schedule in random permuted blocks with stratification by site

1
2
3 251 (22). There will be no blinding of the randomization assignment.

4 252

5 253 *Endpoints*

6 254 Clinically relevant access site related bleeding or vascular complication requiring intervention
7 255 of the randomized access site during hospitalization is defined as primary endpoint. Bleeding
8 256 will be classified according to the Bleeding Academic Research Consortium (BARC) criteria
9 257 (23), and considered clinically relevant when the score is ≥ 2 (CEC adjudicated)(24). Severity
10 258 and type of intervention of vascular complications is specified in the CEC manual
11 259 (Supplementary file I).

12 260 Secondary safety and efficacy endpoints are:

13 261 - Procedural success (defined as successful PCI of the target lesion with a residual stenosis of
14 262 less than 20%, without in-hospital MACE), procedural time, fluoroscopy time, contrast use
15 263 and crossover rate (crossover is defined as conversion from TF to TR or vice versa;
16 264 conversion to contralateral TR or TF access site is not considered crossover).

17 265 - Clinically relevant BARC bleedings or vascular complications (requiring intervention) that
18 266 are not related to the randomized access (CEC adjudicated)

19 267 - MACE, defined as composite of death, MI and repeat revascularization, during
20 268 hospitalization and at 1 month (CEC adjudicated)

21 269

22 270 *Index percutaneous coronary intervention and hospitalization*

23 271 Radial access will be performed according to the local protocol, using direct needle technique
24 272 or venous cannula technique, followed by introduction of a 7 Fr Glidesheath Slender. A
25 273 standard cocktail of nitroglycerine and verapamil will be given intra-arterially after radial
26 274 sheath placement. Femoral access will be performed using direct needle technique, followed
27 275 by introduction of a standard 7 Fr femoral sheath. Use of ultrasound for vascular access will
28 276 be left to the operator's discretion. A bolus of unfractionated heparin will be given after
29 277 sheath placement, adapted to the patient's body weight. Activated clotting time (ACT)
30 278 measurements will be performed during the procedure according to local protocol. Additional
31 279 arterial access will be left to the discretion of the operator, i.e. in case of double arterial access
32 280 for hybrid CTO treatment. In case of randomization to TRA, a 7 Fr Glidesheath Slender must
33 281 be inserted in the right or left radial artery. Then, the operator can decide which secondary
34 282 access site he/she will use and which sheath size is needed for this secondary access. This can
35 283 be the contralateral radial artery (bi-radial approach) or the femoral artery. If the patient is
36 284 randomized to femoral access and needs dual access, a 7 Fr femoral sheath must be placed in
37 285 the femoral artery (randomized access site) and the operator can decide which second access
38 286 he/she will use (radial or femoral). Only clinically significant bleeding or vascular
39 287 complications attributable to the randomized access site will be analyzed for the primary
40 288 endpoint, complications attributable to the secondary access site will be analyzed as
41 289 secondary endpoint. PCI will be performed according to standard procedures with modern
42 290 drug eluting stents. The applied technique for complex PCI will be left to the discretion of the
43 291 operator. Patent hemostasis after radial access with the reverse Barbeau test is highly
44 292 recommended (25). The type of femoral artery hemostasis will be left to the discretion of the
45 293 treating interventional cardiologist; however the application of a closure device is advocated.
46 294 The visual analogue scale (VAS) will be used to assess post-procedural pain of the access
47 295 site(s). Before discharge the access site(s) will be checked for bleeding and vascular
48 296 complications. Radial artery patency will be checked with the reverse Barbeau test (25).

49 297 Additional ultrasound or doppler will be performed in those patients with suspected radial or
50 298 femoral occlusion or the presence of other vascular complications.

51 299

52 300

301 *Extremity dysfunction*

302 Two validated questionnaires will be used to assess the occurrence of upper and lower
303 extremity dysfunction. Upper extremity function will be measured with the QuickDASH
304 (Quick Disabilities of Arm, Shoulder and Hand) score (26) measured at baseline (before PCI)
305 and at 1 month follow-up. Lower extremity function will be measured with the LEFS (Lower
306 Extremity Functional Scale) (27). Both questionnaires are valid, reliable and responsive to
307 monitor and assess pain and function of the extremities.

308 309 *Follow-up*

310 Follow-up will be performed 1 month after index procedure discharge by either phone call or
311 outpatient clinic visit. MACE and access site bleeding or vascular complications will be
312 documented. Extremity function and discomfort will be assessed, using the aforementioned
313 scores. Adverse Events (AE's) will be monitored from inclusion to one-month follow-up and
314 will be assessed by an independent DSMB, composed of two experienced cardiologists and
315 one statistician, reviewing patient safety and study integrity.

316 317 *Sample size calculation and statistics*

318 Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the
319 proportion of access site related bleeding or vascular complication to be 3.5% with radial
320 access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1)
321 will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients
322 will be needed. Data will be analyzed according to the intention-to-treat analysis. All
323 statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically
324 significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago,
325 Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-
326 Square test will also be used for our secondary objectives with binary outcomes. For our
327 secondary objectives with continuous variables we will use the Student's t-test (normally
328 distributed) or the Mann-Whitney U test (non-normally distributed). A pre-specified battery
329 of sub-group analyses will be performed as well, including several independent risk factors
330 for clinically significant bleeding and vascular complications. For demographics and baseline
331 characteristics, these sub-groups consist of age ≥ 75 years, female sex, low body weight
332 (Body Mass Index < 18.5), hypertension, peripheral arterial disease, left ventricular ejection
333 fraction < 30%, severe renal dysfunction (Modification of Diet in Renal Disease (MDRD) <
334 30ml/1.73m²) and pre-existent anemia (hemoglobin <6.8 mmol/l) (13,28–33). For procedural
335 characteristics, sub-group analyses will be performed for use of secondary access site,
336 ultrasound guided puncture, ACT > 150 seconds right before sheath removal and use of
337 closure device (34–37). In addition, primary and secondary endpoints will be specified for the
338 entire population as well as for each group of complex lesions separately (CTO, left main
339 disease, complex bifurcation and heavy calcification). Statistical analysis will be performed
340 by an independent contract research organization (Diagram BV, Zwolle, the Netherlands).

341 342 *Ethics and dissemination*

343 Ethical approval for the study was granted by the local Ethics Committee ('Medisch Ethische
344 Toetsing Commissie Isala Zwolle' for all Dutch sites, 'Commissie voor medische ethiek
345 ZNA' for ZNA Middelheim, 'Comité Medische Ethiek Ziekenhuis Oost-Limburg' for
346 Hospital Oost-Limburg, 'Comité d'éthique CHU-Charleroi – ISPPC' for Centre Hospitalier
347 Universitaire de Charleroi, 'Commission cantonale d'éthique de la recherche CCER –
348 Republique et Canton de Geneve' for Geneva University Hospital, 'Ethik Kommission de
349 Ärztekammer Nordrhein' for Elisabeth-Krankenhaus and 'Riverside Research Ethics
350 Committee' for Frimley NHS) after reviewing the protocol, site-

1
2
3 351 specific informed consent forms (local language and English versions, see also supplementary
4 352 file II), participant education and recruitment materials, other requested documents and any
5 353 subsequent modifications. Trained research nurses or physicians directly involved in the trial
6 354 will introduce the trial to eligible patients. Patients will also receive patient information
7 355 form (PIF). The research nurse or physician will discuss the trial with patients in light of the
8 356 information provided in the PIF and will obtain written consent from patients willing to
9 357 participate in the trial. No reimbursement is provided to study participants. All study-related
10 358 information will be stored securely at the study site. All participant information will be stored
11 359 in locked file cabinets in areas with limited access. All reports, data collection, process, and
12 360 administrative forms will be identified by a coded identification-number only to maintain
13 361 participant confidentiality. All records that contain names or other personal identifiers, such
14 362 as locator forms and informed consent forms, will be stored separately from study records
15 363 identified by code number. All local databases will be secured with password-protected
16 364 access systems. Safety and progress reports to the EC's will be made at least annually and
17 365 within three months of study termination or completion. These reports will include the total
18 366 number of participants enrolled and summaries of the DSMB. Any modifications to the
19 367 protocol which may have impact on the conduct of the study, potential benefit of the patient
20 368 or may affect patient safety, including changes of study objectives, study design, patient
21 369 population, sample sizes, study procedures, or significant administrative aspects will require a
22 370 formal amendment to the protocol. Such amendment will have to be approved by the Ethics
23 371 Committee prior to implementation. The study findings will be disseminated via publication
24 372 of peer-reviewed manuscripts and presentations at international conferences, as well as
25 373 through media publications. Results will be published irrespective of whether the findings are
26 374 positive or negative.

31 375 32 376 *Patient and Public Involvement*

33 377 No patient involved

34 378 35 379 **Discussion**

36 380 TRA is nowadays the standard for PCI, mainly driven by the lower risk of bleeding and
37 381 vascular complications compared to TFA, with even a mortality benefit in ACS patients
38 382 (2,3,38,39). Randomized data in patients with stable coronary artery disease are limited and
39 383 more heterogeneous, and show less beneficial effect of radial over femoral access (1,40,41).
40 384 Moreover, complex coronary lesions are absent or at least not specifically described in most
41 385 trials supporting current guidelines on myocardial revascularization. Currently, the femoral
42 386 artery is still considered the preferred access site for complex PCI by many operators
43 387 (11,16,42–44), despite the increased risk of bleeding and vascular complications, especially
44 388 when large bore guiding catheters (≥ 7 Fr) are required (11,45–48). During CTO-PCI, the use
45 389 of large-bore guiding catheters has been reported in 60-70% of cases and is associated with a
46 390 higher procedural success rate (9,16). Large-bore guiding catheters have better materials'
47 391 compatibility, especially when using guide extensions and microcatheters. The use of
48 392 CrossBoss/Stingray (Boston Scientific, Marlborough, MA, USA) for antegrade dissection/re-
49 393 entry technique is only possible with large-bore guiding catheters (49). Although registries
50 394 show increased temporal adoption of TRA for PCI of heavily calcified lesions with use of
51 395 rotational atherectomy with similar procedural success rates and less bleeding, TFA is still
52 396 used in a large proportion of these procedures, which often mandate large bore guiding
53 397 catheters especially for accommodating larger burr sizes (50,51). Application of large-bore
54 398 guiding catheters for complex PCI of left main and true bifurcations is advocated by experts,
55 399 though efficacy and safety data are lacking. Limited data show comparable feasibility of TRA
56
57
58
59
60

1
2
3 400 versus TFA for left main as well as bifurcation PCI with a tendency towards less bleeding
4 401 complications (11,52–58).

5 402
6 403 The most important argument to refrain from TR PCI for complex coronary lesions is the
7 404 limited diameter of the radial artery. Current standard 7 Fr radial sheaths have an outer
8 405 diameter of 2.97-3.19 mm (59). As such, the percentage of patients with a radial artery
9 406 smaller than the outer diameter of a 7 Fr sheath ranges between 29% and 67% in men and
10 407 between 60% up to 85% in women (60). This suggests that using a standard 7 Fr sheath for
11 408 TRA will result in sheath to artery mismatch in a significant proportion of patients, increasing
12 409 the risk of vascular complications. Radial artery occlusion (RAO) is the most frequent
13 410 complication after radial access, with increasing RAO rates with increasing sheath size (61).
14 411 In most instances, RAO will not lead to any clinical sequelae, however in rare cases RAO
15 412 may require intervention because of extremity dysfunction or ischemia (62,63). Moreover,
16 413 RAO prohibits future re-cannulation of the radial artery, harvesting the radial artery as
17 414 conduit for CABG or creating a hemodialysis shunt (64). Other arguments to use the femoral
18 415 artery for complex PCI have been suggested, such as improved back-up with potential higher
19 416 procedural success rates and shorter procedural time and lower radiation dose. However, this
20 417 is not supported by observational data showing similar effectiveness, procedural success rates,
21 418 cross-over rates, radiation dose and contrast use for TRA and TFA (11,16,17,39).
22 419 Several technologies have been developed to facilitate large bore access through the radial
23 420 artery (65). A sheathless approach for example was shown to be a feasible alternative for
24 421 large bore radial access (66). The 7.5 Fr Eaucath sheathless guiding catheter (ASAHI Intecc,
25 422 Aichi, Japan) has the same inner diameter as a regular 7 Fr guiding catheter, but an outer
26 423 diameter of 2.49 mm, resulting in a large reduction in outer diameter (approximately 2 Fr)
27 424 compared with a standard 7 Fr sheath (67). However, PCI with sheathless guiding catheters
28 425 requires specific experience due to the highly hydrophilic coating, and limited evidence exists
29 426 regarding the true impact on RAO (68,69). Miniaturization of TR equipment can also be
30 427 achieved through a sheath-based approach. Thanks to a reduction in sheath wall thickness
31 428 (“slender technology”), thin-walled sheaths have reduced their outer diameter while
32 429 maintaining the same inner diameter. The 7 Fr Glidesheath Slender (Terumo, Japan) is the
33 430 first commercially available 7 Fr thin-walled sheath, combining an inner diameter of 2.46mm,
34 431 compatible with any 7 Fr guiding catheter, with a reduced outer diameter of 2.79mm. A recent
35 432 prospective multicenter study has shown the feasibility and safety of using the 7 Fr
36 433 Glidesheath Slender for complex TR-PCI in daily practice with a high rate of procedural
37 434 success and low rate of vascular complications (14).
38 435

39 436 In the literature, several outcome measures have been used to evaluate access site related
40 437 bleeding complications, such as the Thrombolysis in Myocardial Infarction (TIMI)(70), the
41 438 Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary
42 439 arteries (GUSTO)(71) or BARC (23). Access site hematoma size has also been used as an
43 440 outcome measure in studies comparing radial with femoral access. BARC bleeding ≥ 2 has
44 441 shown to independently predict 1-year mortality and capture more clinically significant
45 442 bleeding than TIMI minor/major and GUSTO moderate/severe criteria (23,24). Importantly,
46 443 hematoma size alone, not meeting criteria for other bleeding outcome measures, has not
47 444 shown any association with clinically relevant endpoints (72). The current trial will use the
48 445 BARC bleeding score for the primary outcome measure to detect a clinically relevant
49 446 difference in bleedings between TRA and TFA for complex PCI, adjudicated by a CEC.
50 447 Besides bleeding and vascular complications, vascular access may also have a potential effect
51 448 on extremity function (73,74). Although upper extremity dysfunction is present in a small
52 449 proportion of patients after TRA, it can lead to important morbidity for the affected patients

1
2
3 450 (73–76). Extremity dysfunction may be more pronounced in patients with large-bore access.
4 451 In addition, current literature does not provide an insight around prevalence and significance
5 452 of lower extremity function after TFA (74). Therefore, we will assess the occurrence of
6 453 extremity dysfunction utilizing the QuickDASH and LEFS questionnaires, which will be
7 454 valuable information for both patients and doctors.
8 455

9 456 In conclusion, The COLOR trial is the first prospective multicenter randomized trial
10 457 comparing TRA with TFA using large-bore guiding catheters for complex PCI. Currently 290
11 458 patients are randomized. The results of this trial will provide important insights about the
12 459 safety and efficacy of large-bore TRA and TFA for complex PCI. If this trial can show that
13 460 TRA is not only as effective but also safer (less clinically relevant bleeding and vascular
14 461 complications) in complex large bore PCI, it has a potential impact on daily practice.
15 462

16 463 **Contributorship statement**

17 464 Maarten van Leeuwen and Adel Aminian substantially contributed to conception and design
18 465 of the study protocol. Thomas Meijers, Adel Aminian, Koen Teeuwen, Marleen van Wely,
19 466 Thomas Schmitz, Rene van der Schaaf, Maurits Dirksen, Juan Iglesias, Pierfrancesco
20 467 Agostoni, Joseph Dens, Paul Knaapen, Sudhir Rathore and Maarten van Leeuwen contributed
21 468 to acquisition of data. Thomas Meijers, Adel Aminian and Maarten van Leeuwen contributed
22 469 to analysis of data. Thomas Meijers, Adel Aminian, Maarten van Leeuwen and Niels van
23 470 Royen contributed to interpretation of data. Thomas Meijers, Adel Aminian and Maarten van
24 471 Leeuwen reviewed the literature, contributed to the design and wrote the draft of the
25 472 manuscript. Thomas Meijers, Adel Aminian, Koen Teeuwen, Marleen van Wely, Thomas
26 473 Schmitz, René van der Schaaf, Maurits Dirksen, Juan Iglesias, Pierfrancesco Agostoni, Joseph
27 474 Dens, Paul Knaapen, Sudhir Rathore, Jan Paul Ottervanger, Jan Henk Dambrink, Vincent
28 475 Roolvink, Marcel Gosselink, Renicus Hermanides, Niels van Royen and Maarten van
29 476 Leeuwen contributed to refinement of the study protocol and approved the final manuscript.
30 477
31 478

32 479 **Reference list**

- 33 480
34 481
35 482
36 483
37 484
38 485
39 486
40 487
41 488
42 489
43 490
44 491
45 492
46 493
47 494
48 495
49 496
50 497
51 498
52 499
1. Ferrante G, Rao S V., Jüni P, Da Costa BR, Reimers B, Condorelli G, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2016;
 2. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet.* 2011;
 3. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet.* 2018;
 4. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg.* 2019;
 5. Ferrante G, Rao S V., Jüni P, Da Costa BR, Reimers B, Condorelli G, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2016;9(14):1419–34.

- 1
2
3 500 6. Santas E, Bodí V, Sanchis J, Núñez J, Mainar L, Miñana G, et al. The Left Radial
4 501 Approach in Daily Practice. A Randomized Study Comparing Femoral and Right and
5 502 Left Radial Approaches. *Rev Española Cardiol (English Ed)*. 2009;
- 6 503 7. Louvard Y, Benamer H, Garot P, Hildick-Smith D, Loubeyre C, Rigattieri S, et al.
7 504 Comparison of transradial and transfemoral approaches for coronary angiography and
8 505 angioplasty in octogenarians (the OCTOPLUS study). *Am J Cardiol*. 2004;
- 9 506 8. Burzotta F, De Vita M, Lefevre T, Tommasino A, Louvard Y, Trani C. Radial
10 507 approach for percutaneous coronary interventions on chronic total occlusions:
11 508 Technical issues and data review. *Catheterization and Cardiovascular Interventions*.
12 509 2014.
- 13 510 9. Tanaka Y, Moriyama N, Ochiai T, Takada T, Tobita K, Shishido K, et al. Transradial
14 511 Coronary Interventions for Complex Chronic Total Occlusions. *JACC Cardiovasc*
15 512 *Interv*. 2017;
- 16 513 10. Galassi AR, Tomasello SD, Reifart N, Werner GS, Sianos G, Bonnier H, et al. In-
17 514 hospital outcomes of percutaneous coronary intervention in patients with chronic total
18 515 occlusion: Insights from the ERCTO (European Registry of Chronic Total Occlusion)
19 516 registry. *EuroIntervention*. 2011;
- 20 517 11. Chung S, Her SH, Song PS, Song Y Bin, Hahn JY, Choi JH, et al. Trans-radial versus
21 518 trans-femoral intervention for the treatment of coronary bifurcations: Results from
22 519 coronary bifurcation stenting registry. *J Korean Med Sci*. 2013;
- 23 520 12. Smilowitz NR, Kirtane AJ, Guiry M, Gray WA, Dolcimascolo P, Querijero M, et al.
24 521 Practices and complications of vascular closure devices and manual compression in
25 522 patients undergoing elective transfemoral coronary procedures. In: *American Journal of*
26 523 *Cardiology*. 2012.
- 27 524 13. Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, et al. Incidence,
28 525 predictors, and prognostic implications of bleeding and blood transfusion following
29 526 percutaneous coronary interventions. *Am J Cardiol*. 2003;
- 30 527 14. Aminian A, Iglesias JF, Van Mieghem C, Zuffi A, Ferrara A, Manih R, et al. First
31 528 prospective multicenter experience with the 7 French Glidesheath slender for complex
32 529 transradial coronary interventions. *Catheter Cardiovasc Interv*. 2017;
- 33 530 15. Megaly M, Karatasakis A, Abraham B, Jensen J, Saad M, Omer M, et al. Radial Versus
34 531 Femoral Access in Chronic Total Occlusion Percutaneous Coronary Intervention. *Circ*
35 532 *Cardiovasc Interv*. 2019;
- 36 533 16. Jan Bakker E, Maeremans J, Zivelonghi C, Faurie B, Avran A, Walsh S, et al. Fully
37 534 transradial versus transfemoral approach for percutaneous intervention of coronary
38 535 chronic total occlusions applying the hybrid algorithm insights from recharge registry.
39 536 *Circ Cardiovasc Interv*. 2017;
- 40 537 17. De Maria GL, Burzotta F, Trani C, Kassimis G, Pirozzolo G, Patel N, et al. Trends and
41 538 Outcomes of Radial Approach in Left-Main Bifurcation Percutaneous Coronary
42 539 Intervention in the Drug-Eluting Stent Era: A Two-Center Registry. *J Invasive Cardiol*.
43 540 2015;
- 44 541 18. Rathore S, Hakeem A, Pauriah M, Roberts E, Beaumont A, Morris JL. A comparison
45 542 of the transradial and the transfemoral approach in chronic total occlusion percutaneous
46 543 coronary intervention. *Catheter Cardiovasc Interv*. 2009;
- 47 544 19. Stone GW, Reifart NJ, Moussa I, Hoyer A, Cox DA, Colombo A, et al. Percutaneous
48 545 recanalization of chronically occluded coronary arteries: A consensus document - Part
49 546 II. *Circulation*. 2005.
- 50 547 20. Sianos G, Morel M-A, Kappetein AP, Morice M-C, Colombo A, Dawkins K, et al. The
51 548 SYNTAX Score: an angiographic tool grading the complexity of coronary artery
52 549 disease. *EuroIntervention*. 2005;
- 53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 550 21. Zlotnick DM, Ramanath VS, Brown JR, Kaplan A V. Classification and treatment of
551 coronary artery bifurcation lesions: Putting the Medina classification to the test.
552 *Cardiovasc Revascularization Med.* 2012;
- 553 22. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials.
554 *Control Clin Trials.* 1988;
- 555 23. Mehran R, Rao S V., Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al.
556 Standardized bleeding definitions for cardiovascular clinical trials: A consensus report
557 from the bleeding academic research consortium. *Circulation.* 2011;
- 558 24. Vranckx P, White HD, Huang Z, Mahaffey KW, Armstrong PW, Van De Werf F, et al.
559 Validation of BARC Bleeding Criteria in Patients with Acute Coronary Syndromes the
560 TRACER Trial. *J Am Coll Cardiol.* 2016;
- 561 25. Wilson SJ, Mitchell A, Gray TJM, Loh HJ, Cruden NL. Patent haemostasis prevents
562 radial artery occlusion in patients with an acute coronary syndrome. *Int J Cardiol.*
563 2017;
- 564 26. Beaton DE, Wright JG, Katz JN, Amadio P, Bombardier C, Cole D, et al. Development
565 of the QuickDASH: Comparison of three item-reduction approaches. *J Bone Jt Surg -*
566 *Ser A.* 2005;
- 567 27. Binkley J, Stratford P, Lott S, Riddle D. The lower extremity functional scale. *Phys*
568 *Ther.* 1999;
- 569 28. Numasawa Y, Kohsaka S, Ueda I, Miyata H, Sawano M, Kawamura A, et al. Incidence
570 and predictors of bleeding complications after percutaneous coronary intervention. *J*
571 *Cardiol.* 2017;
- 572 29. Numasawa Y, Kohsaka S, Miyata H, Kawamura A, Noma S, Suzuki M, et al. Impact of
573 body mass index on in-hospital complications in patients undergoing percutaneous
574 coronary intervention in a Japanese real-world multicenter registry. *PLoS One.* 2015;
- 575 30. Singh M, Lennon RJ, Darbar D, Gersh BJ, Holmes DR, Rihal CS. Effect of peripheral
576 arterial disease in patients undergoing percutaneous coronary intervention with
577 intracoronary stents. *Mayo Clin Proc.* 2004;
- 578 31. Ndrepepa G, Groha P, Lahmann AL, Lohaus R, Cassese S, Schulz-Schüpke S, et al.
579 Increased bleeding risk during percutaneous coronary interventions by arterial
580 hypertension. *Catheter Cardiovasc Interv.* 2016;
- 581 32. Mamas MA, Anderson SG, O’Kane PD, Keavney B, Nolan J, Oldroyd KG, et al.
582 Impact of left ventricular function in relation to procedural outcomes following
583 percutaneous coronary intervention: Insights from the British Cardiovascular
584 Intervention Society. *Eur Heart J.* 2014;
- 585 33. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, et al.
586 Defining high bleeding risk in patients undergoing percutaneous coronary intervention:
587 a consensus document from the Academic Research Consortium for High Bleeding
588 Risk. *European Heart Journal.* 2019.
- 589 34. Seto AH, Abu-Fadel MS, Sparling JM, Zacharias SJ, Daly TS, Harrison AT, et al.
590 Real-time ultrasound guidance facilitates femoral arterial access and reduces vascular
591 complications: FAUST (Femoral Arterial Access with Ultrasound Trial). *JACC*
592 *Cardiovasc Interv.* 2010;
- 593 35. Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation.* 2011;
- 594 36. Kern MJ. *Interventional Cardiac Catheterization Handbook.* Interv Card Catheter
595 *Handb.* 1977;
- 596 37. Tavris DR, Wang Y, Jacobs S, Gallauresi B, Curtis J, Messenger J, et al. Bleeding and
597 vascular complications at the femoral access site following percutaneous coronary
598 intervention (PCI): An evaluation of hemostasis strategies. *J Invasive Cardiol.* 2012;
- 599 38. Bernat I, Horak D, Stasek J, Mates M, Pesek J, Ostadal P, et al. ST-segment elevation

- 1
2
3 600 myocardial infarction treated by radial or femoral approach in a multicenter
4 601 randomized clinical trial: The STEMI-RADIAL trial. *J Am Coll Cardiol.* 2014;
5 602 39. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, et al.
6 603 Radial versus femoral randomized investigation in st-segment elevation acute coronary
7 604 syndrome: The rifle-steacs (radial versus femoral randomized investigation in st-
8 605 elevation acute coronary syndrome) study. *J Am Coll Cardiol.* 2012;
9 606 40. Diehl D, de Ribamar Costa J, Costa R, de Mello BG, Chamié D, Jatene T, et al.
10 607 Propensity-score comparison of patients with stable coronary artery disease undergoing
11 608 percutaneous coronary intervention by radial versus femoral approach. *J Am Coll*
12 609 *Cardiol.* 2016;
13 610 41. Rao S V., Hess CN, Barham B, Aberle LH, Anstrom KJ, Patel TB, et al. A registry-
14 611 based randomized trial comparing radial and femoral approaches in women undergoing
15 612 percutaneous coronary intervention: The SAFE-PCI for women (study of access site
16 613 for enhancement of PCI for women) trial. *JACC Cardiovasc Interv.* 2014;
17 614 42. Koifman E, Gaglia MA, Escarcega RO, Bernardo NL, Lager RA, Gallino RA, et al.
18 615 Comparison of transradial and transfemoral access in patients undergoing percutaneous
19 616 coronary intervention for complex coronary lesions. *Catheter Cardiovasc Interv.* 2017;
20 617 43. Alaswad K, Menon R V., Christopoulos G, Lombardi WL, Karpaliotis D, Grantham
21 618 JA, et al. Transradial approach for coronary chronic total occlusion interventions:
22 619 Insights from a contemporary multicenter registry. *Catheter Cardiovasc Interv.* 2015;
23 620 44. Watt J, Austin D, Mackay D, Nolan J, Oldroyd KG. Radial Versus Femoral Access for
24 621 Rotational Atherectomy: A UK Observational Study of 8622 Patients. *Circ Cardiovasc*
25 622 *Interv.* 2017;
26 623 45. Doyle BJ, Ting HH, Bell MR, Lennon RJ, Mathew V, Singh M, et al. Major Femoral
27 624 Bleeding Complications After Percutaneous Coronary Intervention. Incidence,
28 625 Predictors, and Impact on Long-Term Survival Among 17,901 Patients Treated at the
29 626 Mayo Clinic From 1994 to 2005. *JACC Cardiovasc Interv.* 2008;
30 627 46. Goel PK, Jatain S, Khanna R, Pandey CM. Left main PCI: An observational analysis
31 628 from large single-centre experience. *Indian Heart J.* 2016;
32 629 47. Gorol J, Tajstra M, Hudzik B, Lekston A, Gąsior M. Comparison of outcomes in
33 630 patients undergoing rotational atherectomy after unsuccessful coronary angioplasty
34 631 versus elective rotational atherectomy. *Postep w Kardiol Interwencyjnej.* 2018;
35 632 48. Kinnaird T, Anderson R, Ossei-Gerning N, Gallagher S, Large A, Strange J, et al.
36 633 Vascular Access Site and Outcomes Among 26,807 Chronic Total Coronary Occlusion
37 634 Angioplasty Cases From the British Cardiovascular Interventions Society National
38 635 Database. *JACC Cardiovasc Interv.* 2017;
39 636 49. Maeremans J, Palmers PJ, Dens J. Initial experience and feasibility of the new low-
40 637 profile stingray catheter as part of the antegrade dissection and re-entry
41 638 revascularization strategy for coronary chronic total occlusions. *Am J Case Rep.* 2017;
42 639 50. Kinnaird T, Cockburn J, Gallagher S, Choudhury A, Sirkar A, Ludman P, et al.
43 640 Temporal changes in radial access use, associates and outcomes in patients undergoing
44 641 PCI using rotational atherectomy between 2007 and 2014: results from the British
45 642 Cardiovascular Intervention Society national database. *Am Heart J.* 2018;
46 643 51. Yin WH, Tseng CK, Tsao TP, Jen HL, Huang WP, Huang CL, et al. Transradial versus
47 644 transfemoral rotablation for heavily calcified coronary lesions in contemporary drug-
48 645 eluting stent era. *J Geriatr Cardiol.* 2015;
49 646 52. Yang YJ, Kandzari DE, Gao Z, Xu B, Chen JL, Qiao S Bin, et al. Transradial versus
50 647 transfemoral method of percutaneous coronary revascularization for unprotected left
51 648 main coronary artery disease: Comparison of procedural and late-term outcomes.
52 649 *JACC Cardiovasc Interv.* 2010;

- 1
2
3 650 53. Kinnaird T, Anderson R, Gallagher S, Sirker A, Ludman P, de Belder M, et al. Access
4 651 Site and Outcomes for Unprotected Left Main Stem Percutaneous Coronary
5 652 Intervention: An Analysis of the British Cardiovascular Intervention Society Database.
6 653 JACC Cardiovasc Interv. 2018;
- 7 654 54. Ziakas A, Klinke P, Mildenerger R, Fretz E, Williams MB, Della Siega A, et al.
8 655 Comparison of the Radial and Femoral Approaches in Left Main PCI: A Retrospective
9 656 Study. J Invasive Cardiol. 2004;
- 10 657 55. Gao Z, Xu B, Yang Y, Kandzari DE, Sun Z, Qiao S, et al. Transradial versus
11 658 transfemoral method of two-stent implantation for true bifurcation lesions: Comparison
12 659 of immediate and long-term outcomes. J Interv Cardiol. 2014;
- 13 660 56. Hsueh SK, Hsieh YK, Wu CJ, Fang CY, Youssef AA, Chen CJ, et al. Immediate
14 661 results of percutaneous coronary intervention for unprotected left main coronary artery
15 662 stenoses: Transradial versus transfemoral approach. Chang Gung Med J. 2008;
- 16 663 57. Chung S, Yang JH, Choi SH, Song Y Bin, Hahn JY, Choi JH, et al. Transradial versus
17 664 transfemoral intervention for the treatment of left main coronary bifurcations: Results
18 665 from the COBIS (COronary Bifurcation Stenting) II registry. J Invasive Cardiol. 2015;
- 19 666 58. Williams PD, Eichhöfer J, Mamas MA, Arnous S, Fath-Ordoubadi F, Fraser D.
20 667 Transradial intervention via large-bore guide catheters: A study of coronary bifurcation
21 668 disease treatment using the crush technique. J Invasive Cardiol. 2013;
- 22 669 59. Bernat I, Aminian A, Pancholy S, Mamas M, Gaudino M, Nolan J, et al. Best Practices
23 670 for the Prevention of Radial Artery Occlusion After Transradial Diagnostic
24 671 Angiography and Intervention: An International Consensus Paper. JACC:
25 672 Cardiovascular Interventions. 2019.
- 26 673 60. Saito S, Ikei H, Hosokawa G, Tanaka S. Influence of the ratio between radial artery
27 674 inner diameter and sheath outer diameter on radial artery flow after transradial
28 675 coronary intervention. Catheter Cardiovasc Interv. 1999;
- 29 676 61. Kotowycz MA, Džavík V. Radial artery patency after transradial catheterization. Circ
30 677 Cardiovasc Interv. 2012;
- 31 678 62. Rademakers LM, Laarman GJ. Critical hand ischaemia after transradial cardiac
32 679 catheterisation: An uncommon complication of a common procedure. Netherlands Hear
33 680 J. 2012;
- 34 681 63. Ayan M, Smer A, Azzouz M, Abuzaid A, Mooss A. Hand ischemia after transradial
35 682 coronary angiography: Resulting in right ring finger amputation. Cardiovasc
36 683 Revascularization Med. 2015;
- 37 684 64. Amin H. Prevention of radial artery occlusion: It's the right thing to do.
38 685 EuroIntervention. 2015;
- 39 686 65. Kiemeneij F, Yoshimachi F, Matsukage T, Amoroso G, Fraser D, Claessen BE, et al.
40 687 Focus on maximal miniaturisation of transradial coronary access materials and
41 688 techniques by the Slender Club Japan and Europe: An overview and classification.
42 689 EuroIntervention. 2015.
- 43 690 66. Mamas MA, Fath-Ordoubadi F, Fraser DG. Atraumatic complex transradial
44 691 intervention using large bore sheathless guide catheter. Catheter Cardiovasc Interv.
45 692 2008;
- 46 693 67. Fraser D, Mamas MA. Transradial Sheathless Approach for PCI. Current Cardiology
47 694 Reports. 2015.
- 48 695 68. Horie K, Tada N, Isawa T, Matsumoto T, Taguri M, Kato S, et al. A randomised
49 696 comparison of incidence of radial artery occlusion and symptomatic radial artery spasm
50 697 associated with elective transradial coronary intervention using 6.5 Fr SheathLess
51 698 Eaucath Guiding Catheter vs. 6.0 Fr Glidesheath Slender. In: EuroIntervention. 2018.
- 52 699 69. Mohsen A, Alqasrawi M, Shantha GPS, DeZorzi C, Panaich S. Comparison of Radial

- 1
2
3 700 Artery Occlusion Following Transradial Access for Percutaneous Coronary
4 701 Intervention Using Sheath-based versus Sheathless Technique. *Sci Rep.* 2018;
5 702 70. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis
6 703 in myocardial infarction (TIMI) trial, phase I: A comparison between intravenous
7 704 tissue plasminogen activator and intravenous streptokinase. Clinical findings through
8 705 hospital discharge. *Circulation.* 1987;
9 706 71. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute
10 707 Myocardial Infarction. *N Engl J Med.* 1993;
11 708 72. White HD, Aylward PE, Gallo R, Bode C, Steg G, Steinhubl SR, et al. Hematomas of
12 709 at least 5 cm and outcomes in patients undergoing elective percutaneous coronary
13 710 intervention: Insights from the SafeTy and Efficacy of Enoxaparin in PCI patients, an
14 711 international randomized Evaluation (STEEPLE) trial. *Am Heart J.* 2010;
15 712 73. van Leeuwen MAH, Hollander MR, van der Heijden DJ, van de Ven PM, Opmeer
16 713 KHM, Tavernier YJHJ, et al. The ACRA Anatomy Study (Assessment of Disability
17 714 After Coronary Procedures Using Radial Access): A Comprehensive Anatomic and
18 715 Functional Assessment of the Vasculature of the Hand and Relation to Outcome After
19 716 Transradial Catheterization. *Circ Cardiovasc Interv.* 2017;
20 717 74. Ul Haq MA, Rashid M, Kwok CS, Wong CW, Nolan J, Mamas MA. Hand dysfunction
21 718 after transradial artery catheterization for coronary procedures. *World J Cardiol.* 2017;
22 719 75. Ijsselmuiden A, Zwaan E, Kofflard M, Holtzer C. TCT-639 Upper extremity function
23 720 after transradial PCI: preliminary long term results of the ARCUS trial. *J Am Coll*
24 721 *Cardiol.* 2017;
25 722 76. Zwaan EM, Koopman AGMM, Holtzer CAJ, Zijlstra F, Ritt MJPF, Amoroso G, et al.
26 723 Revealing the impact of local access-site complications and upper extremity
27 724 dysfunction post transradial percutaneous coronary procedures. *Netherlands Heart*
28 725 *Journal.* 2015.
29 726
30 727
31 728
32 729

33 728 **Figure legend**

34 729
35 730 Figure 1: Inclusion flowchart for the COLOR trial.

36 731 **Caption:** *Graphic representation of inclusion for the COLOR trial. STEMI = ST elevation*
37 732 *myocardial infarction, BARC = Bleeding Academic Research Group, MACE = Major*
38 733 *Adverse Cardiovascular Events.*
39 734

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

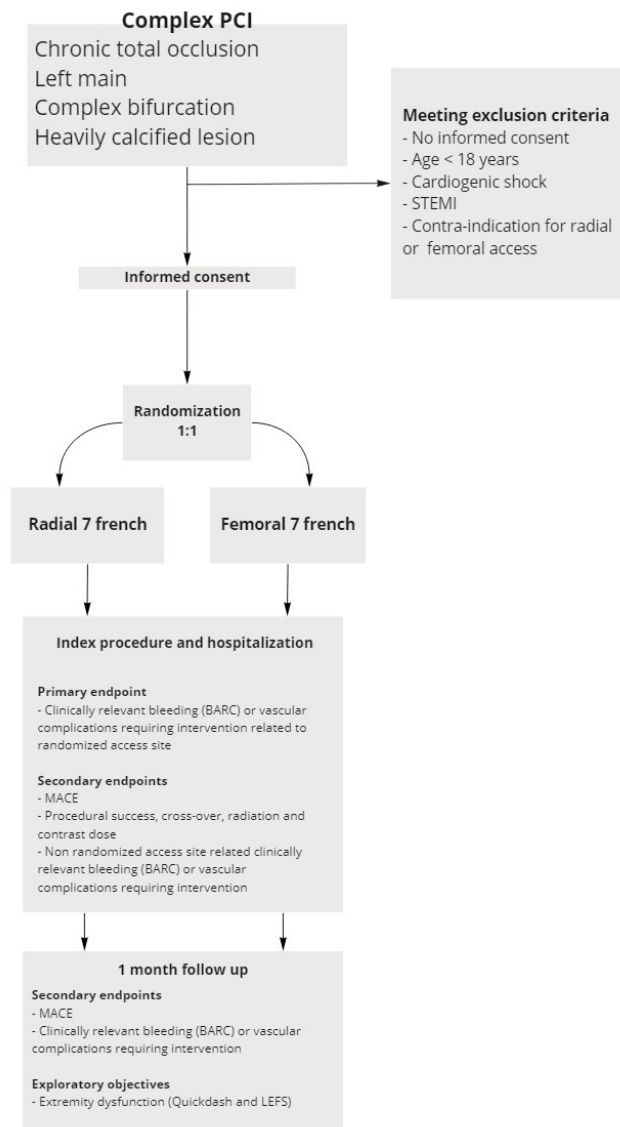


Figure 1: enrollment flowchart of the COLOR trial

300x413mm (72 x 72 DPI)

Supplementary file I: CEC manual for adjudicating bleeding and vascular complications

Classification and Definition

Bleeding

BARC 0

No bleeding or hematoma.

BARC 1

Every bleeding or hematoma not meeting the criteria for BARC 2 or higher.

BARC 2

Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, (prolonged) hospitalization, or treatment by a health care professional.

Specified for radial access and femoral access in this appendix

BARC 3a

Overt bleeding + Hb drop of 3-5 g/dl (1.9 – 3.1 mmol/L), or any transfusion with overt bleeding (independent of Hb)

BARC 3b

Overt bleeding + Hb drop >5g/dl (>3.1 mmol/L), or cardiac tamponade, or bleeding requiring surgical intervention and/or IV vasoactive agents

BARC 3c

Intracranial hemorrhage or intraocular bleedings

BARC 4

CABG related bleeding

BARC 5

Fatal bleeding

Vascular complications

Retroperitoneal hematoma, (pseudo) aneurysm, infection and arteriovenous-fistula or vascular occlusion requiring intervention. Specified for radial access and femoral access in this appendix

Radial access

Specification of BARC 2 bleedings

1. Prolonged hospitalization

Any bleeding that leads to one or more extra hospitalization day(s)

- Based on standard discharge policy of hospital

- For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

2. Additional compression therapy

Any additional compression therapy after successful primary hemostasis

- Bleeding after removal of first TR band and additional compression bandage or TR band is needed

- Ongoing bleeding with first TR band and additional compression therapy is needed

- Adding 1 or 2cc of air in the first TR band due to slight oozing should not be scored as BARC 2

3. Additional investigations

Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

4. Additional therapy

- Any additional or change of therapy related to bleeding/hematoma
- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation of medical therapy (i.e. vitamin K, hematological products)
 - Percutaneous intervention (i.e. coiling)

Specification of vascular complications

- Vascular complications requiring intervention: percutaneous, surgical, medical
- (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
 - Infection (i.e. antibiotics)
 - Arteriovenous-fistula (i.e. percutaneous or surgical intervention)
 - Radial artery occlusion (percutaneous intervention, heparin therapy)
 - Dissection (i.e. percutaneous or surgical intervention)
 - Compartment syndrome (i.e. percutaneous or surgical intervention)

Femoral access

Specification BARC 2 bleeding

1. Prolonged hospitalization

- Any bleeding that leads to one or more extra hospitalization day(s)
- Based on standard discharge policy of hospital
 - For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

2. Additional compression therapy

- Any additional compression therapy after successful primary hemostasis:
- New compression therapy after removal of the first bandage, or additional compression after closure device
 - Prolonging compression bandage due to slight oozing should not be scored BARC 2, when this will not lead to prolonged hospitalization (one or more days).

3. Additional investigations

- Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, angiography or CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

4. Additional therapy

- Any additional or change of therapy related to bleeding/hematoma
- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation medical therapy (i.e. vitamin K, hematological products)
 - Percutaneous intervention (i.e. coiling or stenting of peripheral arteries)

Specification of vascular complications

- 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)

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
- 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)

For peer review only

Supplementary file II

Participation Information Sheet and Consent Form

Centre Number: _____ Patient Number: _____

Study Title: COLOR study - Comparative study of complex Percutaneous Coronary Intervention (PCI) procedures with large catheters through the radial artery or femoral artery.

Principle Investigator: Site specific

Name and Address: Site specific

Telephone: Site specific

Sponsor: ISALA Heart Centre, Zwolle, Netherlands.

1. Introduction

We would like to invite you to take part in this study. Participation is voluntary. If you would like to participate, we need your written consent. Before you decide whether to participate in the study or not, you should know what the study entails. Read this information carefully and ask the researcher for an explanation if you have any questions. If you would like more information, you can also consult the independent expert listed at the end of this letter. You can also discuss it with your partner, friends or family.

2. General information

This study was initiated by the cardiology partnership of the Isala hospital in

1
2
3 Zwolle, and is being conducted by multiple cardiologists in the Netherlands,
4 Belgium, Germany, Switzerland and England. The study requires 388 subjects
5 from different countries.
6

7
8 All research is looked at by an independent group of people called Research Ethics
9 Committee to protect your safety, rights, wellbeing and dignity. This study has been
10 reviewed and given favorable opinion by the local Ethics Committee.
11
12

13 14 **3. Background of the study**

15
16 The radial artery (artery in the arm) is smaller than the femoral artery (artery in the leg).
17 Cardiac catheterization and PCI are already often performed through the radial artery. If
18 the PCI procedure required a thicker catheter because the cardiologist needed more
19 sturdiness to complete it, the groin was often used as the access site due to the larger
20 artery. With the development of a thin-walled radial artery sheath, complex PCI
21 procedures with thicker catheters can now also be performed through the radial artery. A
22 complex PCI procedure through the radial artery may lead to fewer access-site
23 complications than through the femoral artery, while providing a similar PCI result, but
24 this has not yet been properly researched.
25
26
27
28
29
30
31

32 **4. What your participation will entail**

33
34 If you wish to participate, we will first check whether both the groin and the wrist can
35 be used for the PCI procedure.
36

37
38 Before the procedure, we will ask you questions regarding whether or not you can use
39 your arms and legs properly. We will ask you the same questions again one month
40 after the procedure. You will also be asked to complete 2 questionnaires.
41

42
43 If both the radial and femoral arteries can be used, we will randomly assign you,
44 - to determine whether you will be treated through the wrist or the groin.
45

46
47 If you are selected for the wrist procedure, we will use the modern sheath. If you are
48 selected for the groin procedure, we will use the standard sheath.
49

50
51 Aside from the potential difference in sheath, the treatment you will receive will be
52 exactly the same as if you did not participate in the study. The procedure may
53 sometimes require the use of a 2nd catheter. In that case, the cardiologist will
54 determine where the access site for the second catheter will be.
55
56

57
58 The examinations you receive before and after the treatment are also exactly the same
59 as if you did not participate in the study. Those examinations include an
60 electrocardiography (ECG), a blood test and an inspection of the access site (groin or
wrist).

1
2
3
4 The study will require the collection of your medical records for up to one month after
5 the procedure.
6
7

8 **5. What is expected of you?**

9 For a good outcome of the study, it is important that you answer the questions during
10 the study visit and the 1-month check-up to the best of your knowledge.
11
12

13 **6. Possible complications and other/adverse effects/complaints**

14
15 In general, the procedure is performed using standard methods and participation in
16 this study will not result in additional adverse effects. The materials used (including the
17 sheaths) have been approved and are already in use for complex PCI procedures for
18 patients who are not participating in a study. The only inconvenience you may
19 experience is that we will contact you after one month to ask you some questions.
20 Trans-Femoral and Trans-radial access will be performed according to the local protocol
21 with the direct needle technique or venous cannula technique. The complications are
22 the same as standard of care procedure and will be fully covered by the
23 Doctor/Investigator during the discussion before consenting to the procedure.
24 Complications that may arise from inserting and removing a sheath are:
25
26

- 27 -Bleeding
- 28 -Vascular problems
- 29 -Blood vessel closure
- 30
- 31
- 32
- 33
- 34
- 35

36 **7. Possible advantages and disadvantages**

37
38 Before you decide to participate in the study, it is important to consider the possible
39 advantages and disadvantages.
40
41

42 If you participate in the study, there is a chance that you will receive exactly the same
43 treatment as if you were not participating. If you are selected for the treatment group
44 with the modern sheath through the wrist, you may have a reduced chance of
45 accesssite complications, but this has not yet been proven. PCI performed through the
46 femoral artery can also result in a longer hospital stay.
47
48
49
50

51 **8. If you do not wish to participate or wish to end participation in the study**

52 You decide whether or not to participate in the study. Participation is voluntary.
53
54

55 If you do not wish to participate, the PCI procedure with the thicker catheter will be
56 performed in the usual manner. This can be done through the groin or the wrist.
57
58

59 If you do participate, you can change your mind and withdraw at any time, even during
60 the study. You will then receive the standard treatment again. You do not have to
provide a reason for stopping. If the procedure has already begun, it cannot be

1
2
3 reversed and you will also require a follow-up check-up. The data collected up to the
4 moment of withdrawal will be used for the study.
5

6 7 **9. End of the study**

8
9 Your participation in the study ends when:

- 11 You have had the check-up one month after the procedure;
- 12 You choose to stop;

13
14 The researcher feels it is better for you to stop;

15
16 The Isala cardiology partnership, the government or the supervising medical.

17
18 The entire study is complete when all participants are finished.
19

20 21 22 **10. Use and storage of your records**

23
24 All of your records will remain confidential. To protect your privacy, your records will be
25 given a code. Your name and other information which directly identifies you will be
26 omitted. The records can only be traced back to you with the key to the code. Only the
27 study doctor and research staff know which code you have. The study will only ever
28 use your data with that code, never with your name. The key to the code will remain in
29 possession of the study team. Reports on the study will also only use that code.
30
31

32
33
34 Some people will be allowed to access your medical and personal information. Access to
35 your medical and personal Information will be by the study Doctor/Investigator and the
36 research team at site. The Sponsor, representatives of the Sponsor (including the
37 Contract Research Organisation, study monitors, auditors and project manager. Ethics
38 committee and government agencies where permitted or required by law. This is
39 necessary to confirm that the study has been conducted properly and reliably. - They will
40 keep your information confidential. By signing the consent form, you agree to the
41 collection, storage and viewing of your medical and personal records.
42
43
44
45
46
47
48
49
50

51 52 **11. More information on your rights with regard to data processing**

53
54 All the information that is collected during the study is kept confidential and there are
55 strict laws in place which safeguard the privacy of the patient at every stage. We will
56 be using your information (samples and medical records) in order to undertake this
57 study and we will act as the data controller for this study. This means that we are
58 responsible for looking after your information and using it properly. Your identity and
59 contact details will be confidential and all the data collected will be anonymized so you
60 cannot be

1
2
3 identified.

4
5 A description of this study will be available on <http://www.ClinicalTrials.gov>, and this
6 web site will not include information that can identify you.

7 ISALA Heart Centre, Zwolle, is the Sponsor for this study based in the Netherlands.
8 We will be using information from your medical records in order to undertake this
9 study and will act as the data controller for this study. This means that we are for
10 looking after your information and using it properly. ISALA Heart Centre will keep
11 identifiable information about you for 15 years after the study has finished. Your
12 rights to access, change or move your information are limited, as we need to
13 manage your information in specific ways in order for the research to be reliable and
14 accurate. If you withdraw from the study, we will keep the information about you
15 that we have already obtained. To safeguard your rights, we will use the minimum
16 personally identifiable information possible.
17
18
19
20
21

22 The local site will keep your name, ID number and contact details confidential and
23 will not pass this information to ISALA Heart Centre. The local site will use this
24 information as needed, to contact you about the research study, and make sure that
25 relevant information about the study is recorded for you care, and to oversee the
26 quality of the study. Certain individuals from ISALA Heart Centre and regulatory
27 organisations may look at your medical and research records to check the accuracy
28 or the research study. ISALA Heart Centre will only receive information without any
29 identifying information. The people who analyse the information will not be able to
30 identify you and will not be able to find out your name, NHS number or contact
31 details.
32
33
34
35
36
37

38 **12. Insurance for subjects**

39
40 If you participate in the study you will face the same risks as for the standard
41 treatment of your condition. The study is insured with HDI Global SE – UK Policy
42 Number 390-08414363 and has a liability insurance for £5 million.
43
44
45
46

47 **13. Informing your GP**

48
49 We will always notify your GP and/or treating specialist that you are participating in the
50 study. This is for your own safety. If you do not agree to this, you cannot participate in
51 the study. In the event of complications, we may contact your doctor or GP for
52 information such as your medical history or use of medicines.
53
54
55

56 **15. Questions**

57
58 If you have any questions or concerns, please contact the study doctor or the
59 research team.
60

1
2
3 If you have any complaints or require general advice you can contact the hospital's
4 Patient Advice and Liaison Service (PALS).
5

6 **16. Signing the consent form**

7
8
9 Once you have had sufficient time to think about it, you will be asked to decide
10 whether or not to participate in this study. If you consent, we will ask you to confirm
11 your consent in writing on the appropriate consent form. By giving your written
12 consent, you acknowledge that you have understood the information and agree to
13 participation in
14 the study.
15
16

17
18 The signature sheet will be kept by the researcher. You will receive a duplicate or a
19 second copy of the consent form.
20

21
22 Thank you for your reading this information sheet.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Consent form

COLOR trial

- I have read the information letter. I was given the opportunity to ask questions. My questions have been answered to my satisfaction. I have had enough time to decide whether or not to participate. I am aware that participation is voluntary.
- I am also aware that I can decide not to participate or to withdraw from the study at any time. I need not give a reason for this.
- I consent to informing my GP that I am participating in this study.
- I am aware that some people have access to my records. Those people are listed in this information letter.
- I consent to the collection and use of my information in the manner and for the purposes listed in the information letter.
- I consent to the storage of my information at the research site for 15 years after this study.
- I wish to participate in this study.

Name of participant:

Signature:

Date : __ / __ / __

Name of investigator:

Signature:

Date : __ / __ / __



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P
	2b	All items from the World Health Organization Trial Registration Data Set	P 3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	P 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P 1
	5b	Name and contact information for the trial sponsor	P 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P 4
	6b	Explanation for choice of comparators	P 4
Objectives	7	Specific objectives or hypotheses	P 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P 4

Methods: Participants, interventions, and outcomes

1				
2				
3				
4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P 4
5				
6				
7				
8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P 5
9				
10				
11				
12				
13	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 6
14				
15				
16		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
17				
18				
19				
20				
21		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
22				
23				
24				
25		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
26				
27				
28	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P 5
29				
30				
31				
32				
33				
34				
35				
36	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 1
37				
38				
39				
40				
41	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P 6
42				
43				
44				
45	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P 6
46				
47				

Methods: Assignment of interventions (for controlled trials)

Allocation:

51				
52				
53	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P 6
54				
55				
56				
57				
58				
59				
60				

1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	N/A
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	N/A
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	N/A
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13		17b	If blinded, circumstances under which unblinding is permissible, and	N/A
14			procedure for revealing a participant's allocated intervention during	
15			the trial	
16				
17				
18				
19				
20	Methods: Data collection, management, and analysis			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	P 11-12
22	methods		trial data, including any related processes to promote data quality (eg,	
23			duplicate measurements, training of assessors) and a description of	
24			study instruments (eg, questionnaires, laboratory tests) along with	
25			their reliability and validity, if known. Reference to where data	
26			collection forms can be found, if not in the protocol	
27		18b	Plans to promote participant retention and complete follow-up,	P 6
28			including list of any outcome data to be collected for participants who	
29			discontinue or deviate from intervention protocols	
30	Data	19	Plans for data entry, coding, security, and storage, including any	P 6
31	management		related processes to promote data quality (eg, double data entry;	
32			range checks for data values). Reference to where details of data	
33			management procedures can be found, if not in the protocol	
34	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	P 6
35	methods		Reference to where other details of the statistical analysis plan can be	
36			found, if not in the protocol	
37		20b	Methods for any additional analyses (eg, subgroup and adjusted	P 6
38			analyses)	
39		20c	Definition of analysis population relating to protocol non-adherence	N/A
40			(eg, as randomised analysis), and any statistical methods to handle	
41			missing data (eg, multiple imputation)	
42				
43				
44				
45				
46				
47				
48				
49				
50				
51				
52	Methods: Monitoring			
53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	N/A
54			and reporting structure; statement of whether it is independent from	
55			the sponsor and competing interests; and reference to where further	
56			details about its charter can be found, if not in the protocol.	
57			Alternatively, an explanation of why a DMC is not needed	
58				
59				
60				

1				
2		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
3				
4				
5				
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P 4
7				
8				
9				
10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
12				
13				
14				
15	Ethics and dissemination			
16				
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P 7
18				
19				
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P 7-8
21				
22				
23				
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P 7
27				
28				
29		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
30				
31				
32	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P 7
33				
34				
35				
36				
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P 1
38				
39				
40	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
41				
42				
43				
44				
45	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
46				
47				
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P 7
49				
50				
51				
52				
53				
54		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
55				
56				
57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
58				
59				
60				

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp II
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

For peer review only