Rationale and design for the randomized placebo-controlled double-blind trial studying the effect of single antiplatelet therapy (clopidogrel) versus dual antiplatelet therapy (clopidogrel/acetylsalicylic acid) on the occurrence of atherothrombotic events following lower extremity peripheral transluminal angioplasty (CLEAR-PATH)

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ABSTRACT

Rationale Antiplatelet therapy (APT) is the standard of care after endovascular revascularization (EVR) in patients with peripheral artery disease (PAD). APT aims to prevent both major adverse cardiovascular events (MACE) and major adverse limb events (MALE). Nonetheless, the rates of MACE and MALE after EVR remain high. In coronary artery and cerebrovascular disease, dual APT (DAPT)compared to acetylsalicylic acid alone has been proven to reduce MACE without increasing the risk of major bleeding when applied for a restricted number of weeks. However, within the PAD population, insufficient data are available to understand the potential attributable effect of DAPT over single APT (SAPT). Therefore, prospective randomized studies in targeted study populations are warranted.

Trial design CLEAR-PATH is a Dutch multicenter, double-blind, placebo-controlled, randomized trial comparing SAPT (clopidogrel 75 mg plus placebo) with DAPT (clopidogrel 75 mg plus acetylsalicylic acid 80 mg) in patients with PAD undergoing EVR. CLEAR-PATH includes a time-to-event analysis with a follow-up of one year. The primary composite efficacy endpoint consists of all-cause mortality, nonfatal stroke, nonfatal myocardial infarction, severe limb ischemia, (indication for) re-intervention due to any symptomatic restenosis, re-occlusion, or due to acute limb ischemia, and major amputation. The primary safety endpoint contains major bleeding following the Thrombolysis in Myocardial Infarction classification. The enrolment started in August 2022. In total 450 primary efficacy outcome events are required which expectedly amounts to 1696 subjects. Recruitment will take approximately 36 months.

Conclusion CLEAR-PATH will assess the efficacy and safety of DAPT compared to SAPT following EVR in PAD patients.

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Abbreviations: AE, Adverse event; APT, Antiplatelet therapy; ATT, Antithrombotic therapy; ASA, Acetylsalicylic acid; CAD, Coronary artery disease; CVD, Cerebrovascular disease; DAPT, Dual antiplatelet therapy; EVR, Endovascular revascularization; MACE, Major adverse cardiovascular events; MALE, Major adverse limb events; PAD, Peripheral arterial disease; PFT, Platelet function testing; PPI, Proton pump inhibitor; SAPT, Single antiplatelet therapy.

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Background

Peripheral artery disease (PAD) due to atherosclerosis of the lower extremity, is affecting more than 230 million people worldwide and the prevalence will increase.[1,2] PAD relates to a higher risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE). As such, lifelong antiplatelet therapy (APT) in PAD patients is advised. Despite APT, PAD is associated with the highest MACE rate compared to coronary artery disease (CAD) and cerebrovascular disease (CVD).[3] Chronic limb-threatening ischemia (CLTI) is the most severe presentation of PAD and occurs approximately in up to 10% of PAD patients.[4] CLTI patients are mostly offered (endovascular) revascularization (EVR) to prevent progression. After EVR, the rate of MACE and MALE is significantly higher compared to PAD patients without EVR.[5-7] Due to the debilitating symptoms and related high mortality, APT optimization after EVR is recommended.[8-11]

Regarding the choice of APT, the balance between the risk of MACE, MALE, and the risk of (major) bleeding is crucial. For years, clopidogrel or acetylsalicylic acid (ASA) monotherapy has been recommended after EVR in PAD patients.[8,10] In CAD and CVD, dual APT (DAPT) has been shown to decrease the risk of MACE and MALE without increasing the risk of major bleeding compared to ASA.[12-15] However, previous research shows that outcomes of APT in CAD and CVD populations cannot be extrapolated to PAD patients which supports the importance of additional research in this population.[16] Recent guideline and network meta-analysis on antithrombotic therapy (ATT) in symptomatic PAD patients stated that high-quality studies comparing clopidogrel with DAPT after EVR are lacking causing inconclusive advice and heterogeneity in antiplatelet prescription strategies.[8,10,17-19] Consequently, in the Netherlands, clopidogrel monotherapy is preferred. This approach was based on post-hoc sub-analyses of the CAPRIE trial revealing a significant effect of clopidogrel compared with ASA in PAD patients in reducing thrombo-embolic complications.[11,20] However, CAPRIE focused on conservatively treated PAD patients, excluding PAD patients undergoing EVR.

The absence of trials comparing DAPT with SAPT (single APT) after EVR in PAD patients is a significant knowledge gap according to the literature.[18,19] Therefore, the CLEAR-PATH randomized controlled trial (**Cl**opidogr**El**/**A**spi**R**in-based **P**eripheral **A**rtery disease **TH**erapy) will compare SAPT (clopidogrel 75mg and placebo daily) versus DAPT (clopidogrel 75 mg and ASA 80 mg daily) following EVR in PAD patients.

Trial design and population

CLEAR-PATH (EudraCT number: 2021-006611-29) is an investigator-initiated randomized placebo-controlled double-blind multicenter trial in the Netherlands. It will primarily assess the efficacy and safety of DAPT (clopidogrel 75 mg with acetylsalicylic acid 80mg daily) compared with SAPT (clopidogrel 75 mg with placebo daily) by observing the all-cause mortality, nonfatal stroke, nonfatal myocardial infarction, severe limb ischemia, (indication for) re-intervention due to any symptomatic restenosis, re-occlusion or due to acute limb ischemia, and major amputation, and bleeding events within one-year follow-up in PAD patients who underwent EVR (Table 1).

Patients eligible for inclusion have been diagnosed with symptomatic PAD with a need for EVR with or without additional stenting and/or endarterectomy. At least one Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) lesion in the iliac, femoropopliteal, and/or below-the-knee arteries is required.[21] The main exclusion criteria are acute (limb) ischemia, use of anticoagulant therapy, indication for bypass surgery, and/or coagulopathy (Table 2).

Informed consent will be obtained before EVR. Randomization and blood sampling will follow after successful EVR, i.e., if at least the balloon catheter has been unfolded during EVR. Randomization will be performed by using computer-generated randomization that is stratified by center. The blood sample will be used to determine CYP2C19 polymorphism, however, the CYP2C19 data will remain blinded until the end of the trial and then be analyzed as a post-hoc observational sub-study. The first intake of trial medication starts one day after EVR. This event-driven trial dispensed the trial medication for one year. If a primary or secondary efficacy or safety endpoint has been reached, adjustment of ATT regime, i.e., substitution of trial medication with another ATT regimen, is left at the discretion of the local investigator. Long-term follow-up will be obtained in all living subjects including those who discontinue the trial medication regardless of their reason (exception is made for voluntary withdrawal of informed consent and mental changes rendering patients legally incapacitated) (Figure 1).

The CLEAR-PATH trial was approved by the NedMec medical ethics review committee in May 2022. The first enrolment was in August 2022. Currently, 545 patients have been enrolled. The CLEAR-PATH trial has been designed according to the Medical Research Involving Human Subjects Act, the principles of the Declaration of Helsinki, and the Good Clinical Practice. The standard research file has been reviewed by the Medical Research Ethics Committee "NedMec" and the "central committee on research involving human subjects" (CCMO).

Treatment protocol and follow-up procedures

Treatment selection

All subjects will receive open-label Clopidogrel 75 mg daily plus closed-label ASA 80 mg (DAPT) or matching placebo (SAPT) daily. The treatment selection is based on current (inter)national guidelines.[8,11,18] Clopidogrel 75 mg is the preferential choice after an EVR in pa-

Table 1. Efficacy and safety endpoints/parameters

Primary efficacy (combined) endpoint
• All-cause death
• Nonfatal stroke
• Nonfatal myocardial infarction
• Severe limb ischemia
• (Indication for) Re-intervention due to any symptomatic restenosis or re-occlusion or due to acute limb ischemia
• Major amputation (amputation above the ankle) due to reduced perfusion
Secondary efficacy endpoints
• Cardiovascular death, death due to:
○ *Sudden cardiac arrest,*
○ *Acute myocardial infarction,*
○ *Ischemic stroke,*
○ *Heart failure,*
○ *Cardiogenic shock,*
○ *Immediate complications from a cardiovascular procedure, and*
○ *Other cardiovascular causes*
• MACE[28,29]
○ *Nonfatal stroke,*
○ *Nonfatal myocardial infarction,*
○ *Cardiovascular death*
• MALE
○ *Severe limb ischemia,*
○ *(Indication for) Re-intervention due to any symptomatic restenosis or re-occlusion or due to acute limb ischemia,*
○ *The occurrence of major amputation (amputation above the ankle) due to reduced perfusion*
Primary safety endpoint
• Major bleeding according to the TIMI classification[30]
Secondary safety endpoints/parameters
• Any bleeding following the TIMI classification[30]
• Major (class 3b≥) and any bleeding following BARC classification[55]
• Major and any bleeding following ISTH classification[31,33]
Other parameters
• Haematomas (reported by participants or research team)
• Quality of life following the EQ-5D and VascuQoL-6[23,25]
• Adherence following the MARS classification[24]
• Cost-effectiveness by using the iMCQ and iPCQ[26]
• CYP2C19 polymorphism: genetic screening
• Peptic ulcer: peptic ulcers confirmed by an esophagogastroduodenoscopy
• Aneurysma spurium: aneurysm spurium confirmed by imaging
• Minor amputation: amputations of the ankle or lower due to reduced perfusion

MALE = major adverse limb events; MACE = major adverse cardiovascular events; TIMI = Thrombolysis in myocardial infarction; BARC = Bleeding Academic Research Consortium; ISTH = International Society on Thrombosis and Haemostasis; EQ-5D = EuroQol-5 Dimension; MARS = Medication Adherence Report Scale; iMCQ = Medical Consumption Questionnaire.

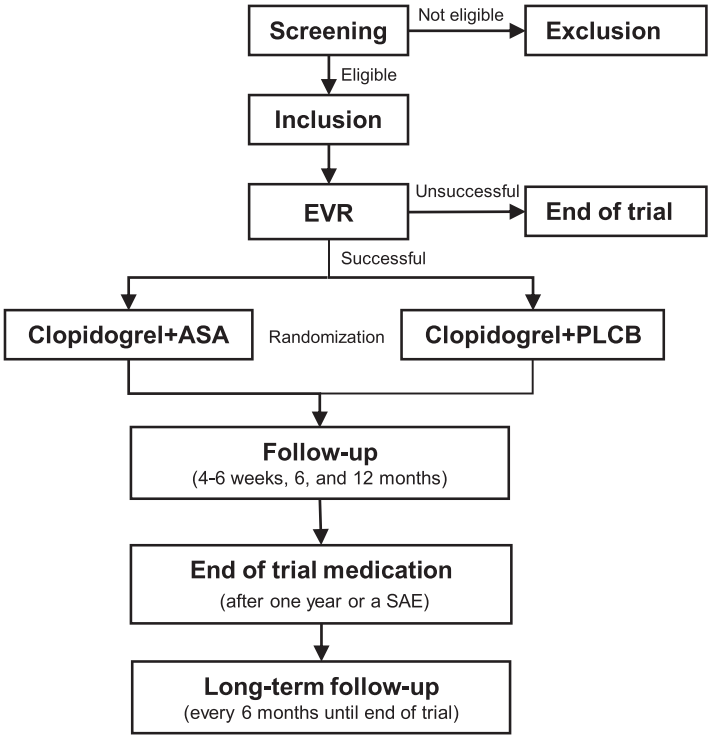
Table 2. In- and exclusion criteria CLEAR-PATH

Inclusion criteria
1. Lesions of the iliac, femoropopliteal, and/or below-the-knee arteries
2. At least one TASC lesion
3. Rutherford 1-6 classes with an indication for an endovascular revascularization
4. Proficient understanding of the consequences of enrolment by the patient
5. Written informed consent by the patient
6. Age ≥ 45 years
And:
7. Eligibility of lesions for;
a. PTA or recanalization with or without additional stenting based on prevailing guidelines, or;
b. Hybrid procedure with an endarterectomy of the common femoral artery and additional iliac, femoral, or tibial PTA, or;
c. A reintervention within 2 months due to a phased treatment
Exclusion criteria
1. Acute (limb) ischemia
2. Reported intolerance or hypersensitivity to the study medications
3. Use of anticoagulant therapy (DOACs or coumarin)
4. Use of NSAIDs >2 weeks which cannot be discontinued
5. Patients incompetent of understanding the consequences of enrolment in the trial
6. Patients with a reintervention due to restenosis/reocclusion within 2 months
7. Patients with a hybrid procedure other than endarterectomy of the common femoral artery such as femoral bypass
8. Patients with coagulopathy
9. Patients with a peptic ulcer confirmed by an esophagogastroduodenoscopy in their medical history
10. Patients who are pregnant/contemplating pregnancy/nursing.
11. Patients requiring dialysis
12. Patients with liver failure and at least one of the following criteria
a. elevated INR value, or;
b. portal hypertension, or;
c. thrombocytopenia <50 × 10^9/L, or;
d. INR, portal tension, or platelet count is unknown

TASC = Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease; PTA = Percutaneous transluminal angioplasty; DOAC = Direct-Acting Oral Anticoagulants; NSAID = non-steroidal anti-inflammatory drugs; INR = International Normalized Ratio.

tients with PAD regarding the Dutch PAD guideline that refers to post-hoc sub-analyses of the CAPRIE trial revealing a significant effect of clopidogrel compared to ASA 325 mg in reducing thrombo-embolic complications in non-post-intervention PAD patients.[11,20] However, following the European Society for Vascular Surgery, DAPT (i.e., clopidogrel 75 mg plus ASA 75 mg), should be considered for a maximum of six months after an EVR which is, likewise, based on underpowered studies and/or non-post-intervention PAD patients, therefore, the given class of recommendation is IIb with the level of evidence "C".[18] Concerning the addition of ASA to clopidogrel, the advised prescription dose in PAD patients is between 75 mg up to 100 mg since a higher dose is not

Figure 1. CLEAR-PATH study design. EVR = endovascular revascularization; ASA = acetylsalicyclic acid; PLCB = placebo; SAE = serious adverse event; APT = antiplatelet therapy.



more effective.[8,11,18,22] In the Netherlands, ASA 80 mg is mostly prescribed and is, therefore, chosen.

In this trial, DAPT or SAPT is dispensed for a maximum of one year. Currently, insufficient data is available to determine the optimal duration of DAPT in PAD patients.[17] Within the field of cardiology, DAPT over one year is rarely considered and if considered, followed by a low class of recommendation due to higher risk of major bleeding without additional MACE prevention.[23,24] Most potential benefit of DAPT is seen within the first 6 months after revascularization. This taken into account, one year of trial medication dispensing is legitimate.

The variety in recommendations between DAPT and SAPT use, results from a knowledge gap and leads to high heterogeneity in the prescription patterns amongst vascular surgeons.[17] Hence, significant interest exists in clarifying this knowledge gap.[19]

Concomitant therapies and recommendations for patients undergoing procedures

Before inclusion, it is mandatory to treat all subjects following the Dutch guideline for cardiovascular risk management and PAD which includes an APT, lipid-lowering therapy, and if needed, antihypertensive.[25] The CLEAR-PATH protocol approves other (pharmacologic) therapies with an exception for non-steroidal anti-inflammatory drugs for longer than 2 weeks and anticoagulant therapy (vitamin-K antagonists and direct oral anticoagulants) (Table 2). When subjects develop an indication for these therapies, withdrawal from the trial medication is required, however, they will participate in the long-term follow-up. To avoid unnecessary peri-hospitalization withdrawal, 2 weeks of cessation of the investigated treatment is accepted, and the use of (prophylactic low-molecular-weight) heparin when hospitalized is allowed. If a proton pump inhibitor (PPI) is prescribed, pantoprazole is preferred to prevent an inhibitory effect on the CYP2C19 enzyme.

Visit schedule and (long-term) follow-up

The CLEAR-PATH trial (long-term) follow-up protocol contains telephone consultations 4-6 weeks and every 6 months after EVR until the end of the study (Figure 1). During this consultation 3 to 5 questionnaires are answered; EuroQol-5 Dimension (EQ-5D), Vascular Quality of Life Questionnaire (VascuQol-6), iMedical Consumption Questionnaire (iMCQ), the Medication Adherence Report Scale (MARS; until 1-year follow-up) and if the subject works, the iProductivity Consumption Questionnaire (iPCQ).[26-30] These questionnaires measure changes in quality of life, costs, and medication adherence over

time. Outpatient visits can be scheduled following the local post-EVR protocol. It is mandatory during every consultation (i.e., outpatient visit or trial follow-up), to assess for any endpoints or other trial-related adverse events (AE; minor amputation, i.e., ankle amputations or lower due to reduced perfusion, non-major bleeding, haematomas, aneurysm spurium, and peptic ulcers).

The long-term follow-up, i.e., telephone consultation after one year, has no direct relation to the primary outcome of this trial. Since little data is available regarding the longer-term outcomes of large PAD cohorts, this trial is considered as a unique opportunity. Therefore, long-term follow-up will be used for sub analyses such as health-care technology assessments.

Total recruitment time will take approximately 36 months while the total duration of this study is estimated at 48 months. The end of the trial is reached when 450 primary efficacy endpoints have been observed or when all subjects have either completed one-year follow-up or experienced a primary efficacy endpoint, whichever comes first.

Study endpoints and other parameters

The primary (composite) efficacy endpoint consists of all-cause mortality, nonfatal stroke, nonfatal myocardial infarction, severe limb ischemia, (indication for) re-intervention due to any symptomatic restenosis, re-occlusion or due to acute limb ischemia, and major amputation (Table 1).[31,32] This large composite of components is considered clinically relevant since all components, barring non-cardiovascular mortality, are common major atherothrombotic complications associated with PAD and are, therefore, attempted to be prevented through the administration of antiplatelet therapy.[8] The secondary efficacy analyses assess whether DAPT is superior to SAPT, in reducing the primary composite endpoint, MACE (i.e., all CAD and CVD events of the primary endpoint along with cardiovascular death), MALE (i.e., all lower-limb events of the primary endpoint), and cardiovascular death alone within 30 days follow-up along with, MACE, MALE and cardiovascular death within 1 year (Table 1). The primary safety endpoint is major bleeding according to the "Thrombolysis In Myocardial Infarction" (TIMI) classification.[33] The TIMI classification is most frequently used as primary safety outcome in comparable trials and is, therefore, preferred to allow accurate comparisons.[19] Secondary safety endpoints are major bleeding according to the "The International Society on Thrombosis and Haemostasis" (ISTH) classification and class 3b or higher following the "Bleeding Academic Research Consortium" (BARC) classification.[34-36]

As secondary safety parameters, any bleeding according to the TIMI, BARC, and ISTH classifications will be registered (Table 1). Non-major bleeding will be registered as an adverse event (AE) along with peptic ulcer, haematomas, aneurysm spurium, and minor amputations (i.e., amputation of the ankle or lower due to reduced perfusion). Furthermore, the CYP2C19 polymorphism results and the patient-reported outcome through the EQ-5D, VascQoL, MARS, iPCQ, and iMCQ questionnaires will be recorded. CYP2C19 polymorphism results will stay blinded until the end of the trial and cannot be used for medication adjustment during long-term follow-up.

Only the primary and secondary efficacy and safety endpoints will be registered along with the trial-related AE. After an endpoint, an additional MARS questionnaire is required and adjustment of ATT regime, i.e., substitution of trial medication with another ATT regimen, is left at the discretion of the local investigator. This allows physicians to start the preferred ATT based on the type of endpoint. However, continuation of the trial medication is preferred for major post-intervention bleeding, i.e., major bleeding within two weeks after any surgical procedure near the incision site, as this is not considered an endpoint. An independent adjudication committee will audit all endpoints and AEs (Appendix I). The adjudicated (S)AE will be used for the statistical analyses. The definition of all endpoints and parameters is given in Table 1.

Statistical considerations

The effect estimate of primary interest is the intention-to-treat hazard ratio for the primary endpoint (time to first occurrence of the combined endpoint of all-cause mortality, nonfatal stroke, nonfatal myocardial infarction, severe limb ischemia, re-intervention due to any symptomatic restenosis, re-occlusion or due to acute limb ischemia, and major amputation), estimated using a stratified Cox proportional hazards model. In the primary analysis, all subjects will be censored 12 months after EVR. The model will be stratified by center, and prognostic variables will be included as covariates (see Table 3). The results will be presented as a hazard ratio with a 95% confidence interval and a p-value. An interim analysis will

Table 3. Prognostic variables

Prognostic variables
• Classification of clinical symptoms (intermittent claudication vs. chronic limb-threatening ischemia, according to the Rutherford classification)
• The type of stenosis (stenosis, occlusion, or both)
• Whether or not the intervention was a multilevel procedure
• Whether or not an intervention in the crural region was part of the overall intervention
• Whether or not an intervention in the iliac region was part of the overall intervention
• Whether or not an intervention in the femoropopliteal region was part of the overall intervention

be performed after 50% of the required primary outcome events, i.e. 225, have been observed.

The sample size is based on the expected combined MACE and MALE rate of 30% within one year for the SAPT arm. This percentage is an estimated mean since the literature shows high variability in MACE and MALE rates.[37-40] An absolute risk reduction (ARR) of 7% in the DAPT group is considered clinically relevant which is slightly higher than comparable trials such as Voyager (ARR 3,75%).[41] Since this patient population has known poor medication adherence,[42] to our opinion, a higher risk reduction is required to obtain a clinically relevant difference. The loss to follow-up rate is estimated at 5%. Assuming constant hazards, 1:1 block randomization, and an alpha of 0.05 (two-sided), 450 primary outcome events are required which expectedly amounts to 848 subjects in each arm to obtain a power of 90%.

The costs and quality-adjusted life-years (QALYs) of DAPT compared to SAPT will be estimated from a healthcare perspective with a lifetime horizon due to the long-term impact of MACE and MALE.[43] The costs and results from the questionnaires will be combined with the long-term effect outcomes obtained from the literature by applying microsimulation model. Outcome measures will be QALYs and Incremental Cost-Effectiveness Ratios including a probabilistic and deterministic sensitivity analysis following the Dutch guidelines for economic evaluations in healthcare.[44]

Study organization

The CLEAR-PATH is an investigator-initiated trial that will be executed in an initial 14 Dutch centers (see Table 1 in Supplementary folder). The sponsor is the University Medical Center Utrecht. The trial steering committee has the final responsibility (Supplementary folder). Coordination and changes in day-to-day strategy are executed by the executive committee. An independent data and safety monitoring board (Appendix I) will examine the trial progress, early efficacy, safety, and will advise the steering committee. The independent adjudication committee will audit all physician-reported endpoints and AE. The CLEAR-PATH study is made possible by a grant from ZorgOnderzoek Nederland (ZonMw; dossier number: 80-84800-98-44023) which is a funding organization based in the Netherlands. See Figure 1 (Supplementary folder) for the governance structure.

CLEAR-PATH is being monitored by clinical research organization Clinical Trial Center Maastricht (CTCM).

Discussion

After lower-extremity EVR, APT is the standard care to prevent MACE and MALE. Current (inter)national PAD guidelines show heterogeneity in their recommendations regarding the APT after EVR due to the absence of significant advantages for one of the APTs in the literature.[8,11,18] Therefore, the CLEAR-PATH trial was designed to compare the efficacy and safety of DAPT (clopidogrel 75 mg plus acetylsalicylic acid 80 mg daily) versus SAPT (clopidogrel 75 mg plus placebo daily) in PAD patients after EVR.

Strength of the trial is the pragmatic follow-up design which allows for easy incorporation into daily practice. The inclusion criteria are designed to include a representative sample of patients suffering from chronic PAD with a need for EVR. All patients will be enrolled in the trial before the EVR to avoid selection bias based on the performance of the EVR. As such the CLEAR-PATH findings are expected to be easily implemented and broadly applicable. Moreover, due to our large sample size and broad inclusion criteria regarding the location of the lesions and severity of the disease, this trial will perform extensive subgroup analyses which may lead to hypothesis-generating leads for future trials. Due to the long-term follow-up which includes cost (iMCQ and iPCQ) and quality-of-life questionnaires (VascuQoL-6 and EQ-5D), extensive data on costs, cost-effectiveness, and patient-reported outcomes are obtained, which is currently lacking in the PAD guidelines.[4,8,10,18] Furthermore, the Netherlands has sophisticated registration systems that allow this trial to retrieve information about hospital visits and cause of death on lost-to-follow-up subjects to reduce the amount of missing data. Last, the CYP2C19 polymorphisms observational sub-analysis of this trial will gain insight into the clinical impact of genetic variation in PAD patients and might be the first step to personalized medicines in patients with PAD.

The CLEAR-PATH trial has some limitations. The Netherlands is a high-income country with a white-dominated population causing a socioeconomic bias. All patients have 5 days after recruitment to consider participation. CLTI patients are, in some cases, treated before this period has expired, inducing an underrepresentation of this group. Moreover, since this trial uses placebo, trial medication is dispensed by hospital pharmacists. Subjects need to pick up their repeat prescription in hospital instead of their local pharmacist or home delivery, leading potentially to a selection and attrition bias. However, there are no additional hospital visits mandatory for the follow-up, keeping effort for participating low, and dispensing repeat prescriptions will in most cases be combined with a mandatory follow-up following the local post-EVR protocol.

As an observational sub-analyses, the clinical influence of CYP2C19 polymorphism on clopidogrel resistance will be studied. Clopidogrel resistance can be verified by genotyping (CYP2C19 polymorphism) or platelet function testing (PFT) that measures platelet aggregation (PA). PFT is affected by multiple variables such as other

diseases, the experience of the clinician, and the time of testing.[45] Therefore, genotyping was chosen for this sub-analyses. The influence of CYP2C19 polymorphism is a widely discussed topic. In theory "poor metabolizers" have a relatively higher risk of getting MACE and MALE than "good metabolizers" when using clopidogrel. However, due to heterogeneous outcomes and study designs, it is unclear whether personalized APT, based on the CYP2C19 enzymes, leads to better outcomes in patients.[46-49] In addition, the majority of these trials did not include PAD patients, highlighting the need for further research in this population.[50,51]

When utilizing the trial medication, no PPI is required as a co-medication which is in accordance with the Dutch branch organization for pharmacists (KNMP).[52] Consideration was given to the Dutch general practitioner guideline (NHG) that recommends a PPI to all subjects aged 70 years and over who receive DAPT.[53] However, the studies used for this guideline show heterogeneous outcomes.[54] A large randomized study that included CAD patients who received DAPT, found a statistically significant difference between a PPI and placebo regarding gastrointestinal bleeding events but the difference in percentages is not clinically relevant (1.8% difference).[55]

Regarding APT, the balance between the risk of a MACE, MALE, and major bleeding is of interest. In theory, SAPT might result in more MACE and MALE while DAPT might lead to more major bleeding events. As stated earlier, research in CAD and CVD proved that DAPT decreases the risk of MACE and MALE without increasing the risk of major bleeding.[12,13] Literature regarding PAD is underpowered and shows slightly different patterns.[18,19] Nevertheless, the current literature shows that DAPT may lead to lower reintervention after a percutaneous transluminal angioplasty within 6 months and prosthetic bypass surgery compared to ASA alone without increasing the risk of major bleeding.[56,57]

To conclude we anticipate that DAPT will reduce the risk of MACE and MALE without increasing the risk of major bleeding in PAD patients undergoing EVR. Consequently, we expect that DAPT will lead to lower overall costs and an increase in the quality of life in PAD patients after EVR. Last, we hypothesize that standardization of genetic testing will not contribute to better clinical outcomes when DAPT is used.

Summary

The CLEAR-PATH trial is a randomized placebo-controlled double-blind investigator-initiated multicenter trial in the Netherlands that will provide strong evidence on the efficacy and safety of dual antiplatelet therapy (Clopidogrel 75 mg/acetylsalicylic acid 80 mg daily) compared to single antiplatelet therapy (Clopidogrel 75 mg daily) in peripheral arterial disease patients who undergo endovascular revascularization.

Conflict of interest

The CLEAR-PATH study is made possible by ZonMw (dossier number: 80-84800-98-44023) which is an independent grant provider. The authors have no (potential) conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2024.04.001.

CRediT authorship contribution statement

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