






Angiographic control versus ischaemia-driven management of patients undergoing percutaneous revascularisation of the unprotected left main coronary artery with second-generation drug-eluting stents: rationale and design of the PULSE trial

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ABSTRACT

Background The role of planned angiographic control (PAC) over a conservative management driven by symptoms and ischaemia following percutaneous coronary intervention (PCI) of the unprotected left main (ULM) with second-generation drug-eluting stents remains controversial. PAC may timely detect intrastent restenosis, but it is still unclear if this translated into improved prognosis.

Methods and analysis PULSE is a prospective, multicentre, open-label, randomised controlled trial. Consecutive patients treated with PCI on ULM will be included, and after the index revascularisation patients will be randomised to PAC strategy performed with CT coronary after 6 months versus a conservative symptoms and ischaemia-driven follow-up management. Follow-up will be for at least 18 months from randomisation. Major adverse cardiovascular events at 18 months (a composite endpoint including death, cardiovascular death, myocardial infarction (MI) (excluding periprocedural MI), unstable angina, stent thrombosis) will be the primary efficacy outcome. Secondary outcomes will include any unplanned target lesion revascularisation (TLR) and TLR driven by PAC. Safety endpoints embrace worsening of renal failure and bleeding events. A sample size of 550 patients (275 per group) is required to have a 80% chance of detecting, as significant at the 5% level, a 7.5% relative reduction in the primary outcome.

Trial registration number NCT04144881

INTRODUCTION

Percutaneous coronary intervention (PCI) of the unprotected left main coronary artery (ULMCA) improves survival and is

not-inferior to surgical revascularisation in most cases.^{1,2} Intrastent restenosis (ISR) is a complication of PCI that negatively impacts prognosis.^{3–5} With currently used second-generation drug-eluting stents (DES-II), ISR is less frequent than with previous stents, and is caused mainly by neoatherogenesis (rather than by neointimal proliferation), which entails a higher risk of destabilisation, acute coronary syndromes (ACS) and stent thrombosis (ST).⁶ ISR may also generate ischaemia, which has a negative prognostic effect in the ULMCA setting. Planned angiographic control (PAC) has been proposed to timely diagnose and treat ISR, but evidence so far collected provides inconclusive results on its benefit.^{7–11} An increased rate of PCI without reduction of cardiovascular events has been mainly reported, but only few studies, limited by low sample size, lack of a randomised design or multivariate adjustment, were focused on ULMCA. In current European Society of Cardiology (ESC) guidelines, PAC after high-risk PCI is a class IIb recommendation, with an inadequate level C of evidence.¹ In this uncertain scenario, PAC following PCI of ULMCA is still performed in many centres. CT coronary (CCT) provides a precise, non-invasive, reconstruction of the coronary tree,

with a very high negative predictive value for significant stenoses and may offer an alternative to invasive coronary angiography.¹² Its use in the PAC setting has been scarcely explored and may provide relevant advantages because of its non-invasiveness. The present study aims to compare a PAC-based follow-up strategy versus conservative management in a prospective, randomised setting. Moreover, the performance of CCT as a diagnostic tool to evaluate ISR of ULMCA, along with its sensibility, specificity, positive and negative predictive value as compared with coronary angiography will also be assessed.

METHODS AND ANALYSIS

Trial hypothesis and outcomes measures

The principal hypothesis of PULSE is that PAC-based management will significantly improve events-free survival in patients undergoing percutaneous revascularisation of ULMCA, as compared with a conservative (symptoms and ischaemia driven) strategy. The study will further evaluate the accuracy of CCT in the evaluation of ISR in the stented ULM. ISR detected with CCT will be confirmed with CA and classified in four patterns according to the Mehran classification (I focal, II intrastent, III proliferative, IV total occlusion).¹³ To date, current DES-II has provided overall similar performances, but very few direct comparisons are available.

Study end-points are defined according to the 2014 American College of Cardiology/American Heart Association Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials report.¹⁴

Primary efficacy end-point: major adverse cardiovascular events (MACE (major adverse cardiovascular events), a composite and mutual exclusive end point including all-cause death, cardiovascular death, myocardial infarction (MI) (excluding periprocedural MI), unstable angina (UA), ST) at 18 months.

Secondary efficacy end-points:

1. Individual components of MACE at 18 months.
2. Target lesion revascularisation (TLR):
 - Any TLR.
 - Any unplanned TLR.
 - TLR driven by PAC.

Safety end-points:

1. Acute kidney injury (AKI) following CCT defined according to the AKI network criteria¹⁵
2. Renal function impairment at 18 months defined as a reduction of glomerular filtration rate of >24% or end-stage chronic kidney disease
3. Any bleeding at 18 months (defined according to Bleeding Academic Research Consortium (BARC) criteria)¹⁶
4. BARC bleedings type III–IV–V at 18 months¹⁶
5. Procedural complications following each PCI: periprocedural MI defined according to the Fourth Universal Definition of Myocardial Infarction¹⁷ arterial access site complications, AKI¹⁵

Trial design

Figure 1 summarises recruitment and study flow. PULSE is a prospective, randomised, controlled trial enrolling consecutive patients of eight Italian tertiary centres (see online supplemental appendix for participating centres) undergoing PCI of ULMCA either for stable coronary artery disease or ACS meeting specific inclusion criteria (see table 1). After the index revascularisation procedure, principal investigators (PIs) at each site confirms the eligibility of a patient and written informed consent is obtained. PIs perform the randomisation lists for each centre, and for prespecified subgroup (ie, patients treated with provisional vs 2-stent strategy¹⁸); subsequently, other cardiologists at each site proceed enrolling participants and randomising patients in a 1:1 fashion to PAC-based management with CCT versus symptoms and ischaemia-driven conservative management according to standard practice. Randomisation is generated through randomly permuted blocks (blocks of eight with <https://www.project-redcap.org/>). Patients' clinical, procedural and outcome data are collected on a dedicated online platform with individualised case report forms warranting anonymisation for each patient enrolled (see online supplemental appendix for data collection).

All patients will undergo a clinical examination 6 months after the enrolment regardless of the arm of assignment. After a run-in period of 6 months, a first censoring of patients' data will be performed and CCT will be executed in the patients randomised to PAC. CCT will be reviewed by at least two independent radiologists (AD, CG and PF) for patients enrolled in the coordinating centre. CCT performed in other participating centres will be assessed by the local radiologist and then re-evaluated by two of the three radiologists of the coordinating centre (AD, CG and PF), thus working as a core lab. Any disagreement will be resolved by a third reviewer or consensus-based discussion. Coronary angiography will be executed in case of significant stenosis of ULM at CCT (angiographic stenosis >50%). PCI will be performed if confirmation of significant stenosis at coronary angiography (angiographic stenosis >50%, fractional flow reserve (FFR) <0.80,¹⁹ intravascular ultrasound (IVUS) minimum luminal area (MLA) <5 mm²⁰). If any significant stenosis (de novo or ISR) is detected in a different site than the ULM, management will be conducted according to the current ESC guidelines on myocardial revascularisation.¹ Following the 6 months run-in period and the execution of the CCT and coronary angiography/PCI where indicated, patients will be followed up for further 12 months (total follow-up 18 months). The final follow-up assessment will be performed by medical examination, medical records review, telephonic contact.

Blinding

Given the nature of CCT and PCI, this is an open-label trial. Researchers performing clinical or telephonic follow-up and adjudicating trial outcomes will not be blinded to treatment assigned. However, a central

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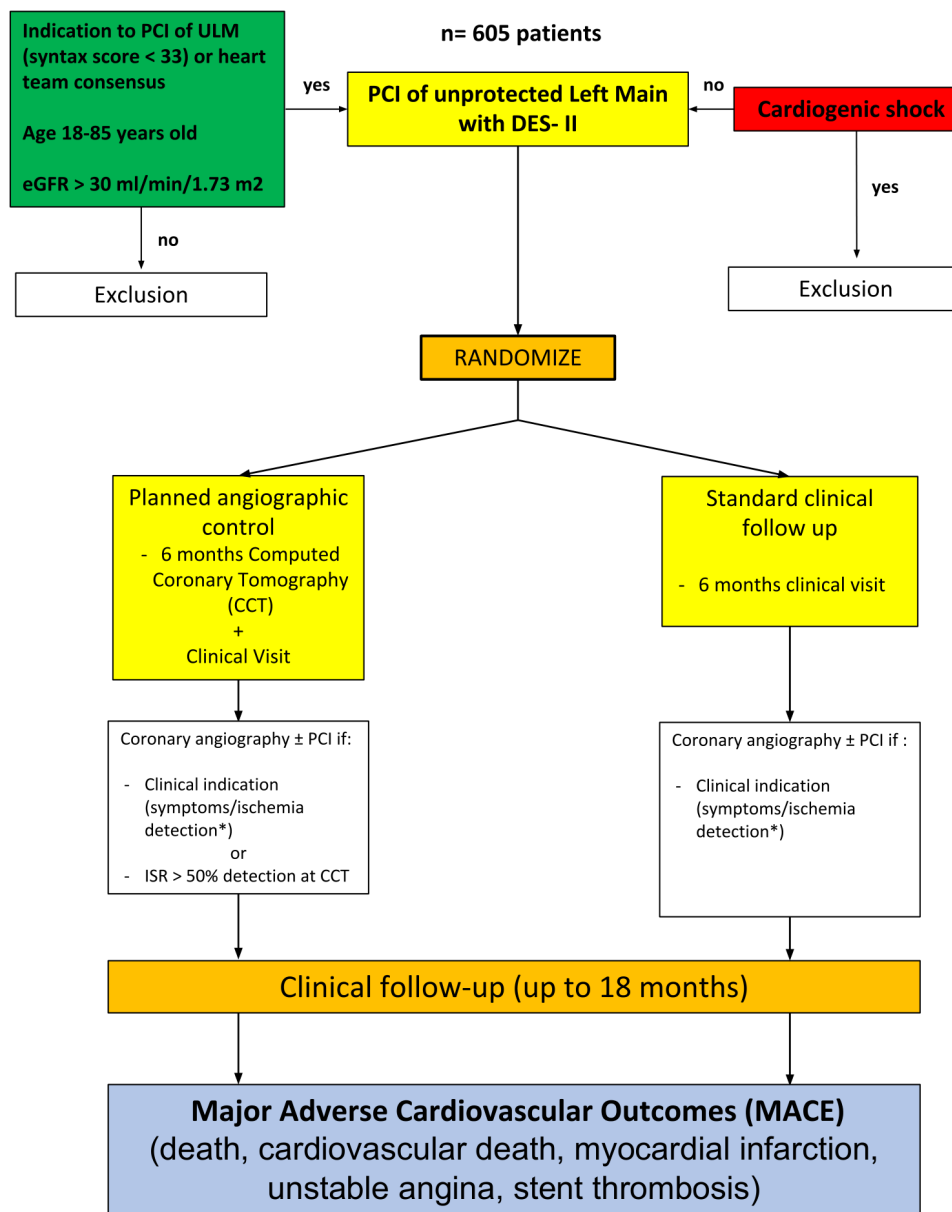


Figure 1 Study flow. *With non-invasive tests (ie, myocardial SPECT; ergometric stress test; dobutamine stress echocardiography) performed according to physicians' indication. DES-II, second-generation drug-eluting stent; EGFR, estimated glomerular filtration rate; ISR, intrastent restenosis; PCI, percutaneous coronary intervention; SPECT, single photon emission computed tomography.

committee composed by PIs blinded to patient data and arm of randomisation will review all the adjudicated outcomes and, where necessary, end-points will be readjudicated.

Statistical considerations

Power calculation

The study by Lee *et al* demonstrated a rate of ISR with DES-II on ULM of 17.6%.⁹ The study of Buchanan *et al* reported a 2-year rate of MACE following ULM PCI with

DES-II of 19.6%.²¹ Assuming a follow-up of 18 months, a sample size of 550 patients (275 per group) is required to have 80% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure by 7.5% (MACE rate 15% for conservative management group vs 7.5% for the PAC group). Assuming a 10% drop-out rate, the total sample size would be 605 patients. Enrolment is planned to be equally distributed among the eight centres.

Table 1 Inclusion and exclusion criteria of the trial**Patients with ULM disease treated by PCI with DES-II**

Inclusion criteria	Exclusion criteria
<ol style="list-style-type: none"> 1. Age 18–85 years old 2. Glomerular filtration rate >30 mL/min/1.73 m²* 3. Indication to percutaneous revascularisation of ULM according to Syntax score (<33) or, in dubious cases, after heart team evaluation 	<ol style="list-style-type: none"> 1. Cardiogenic shock 2. Refusal or inability to provide informed consent

*According to Chronic Kidney Disease Epidemiology Collaboration equation.

DES-II, second-generation drug-eluting stents; PCI, percutaneous coronary intervention; ULM, unprotected left main coronary artery.

Statistical analysis

A detailed statistical analysis plan will be finalised before any data are analysed by treatment assignment. Analysis of outcomes will be by treatment assignment, on an intention-to-treat basis (as treated analysis will be also performed). An unadjusted time-to-event analysis will be performed on the primary outcome using all follow-up data, with time-to-first-event (or censoring) times measured from randomisation. HRs, together with associated CIs, will be calculated from the Cox proportional hazards model. Cumulative event rates will be calculated and presented using Kaplan-Meier time-to-event curves. As a measure of absolute treatment difference, cumulative event rates will be compared at 18 months. Each individual component of the primary composite outcome, as well as other secondary time-to-event outcomes, will be analysed using these methods. Losses to follow-up are expected to be minimal, and patients will be included up until the time they experience the event or are censored. Any categorical data will be expressed as numbers (absolute and percentages) and compared with the use of χ^2 test. Continuous variables will be analysed and presented as mean (along with SD) or median (and quartiles) and compared with analysis of variance test.

An interim analysis after 18 months from the first enrolment will be conducted for safety purposes to exclude a significant early advantage (or disadvantage) of the PAC strategy. A limited number of subgroups analyses will be performed, which will be detailed in the analysis plan. A risk model will be developed, based on interactions between variables and treatment in the Cox model, and used to examine whether the impact of treatment depends on a personal patient's underlying risk.

Procedural features

Computed coronary angiography

CCT will be executed in patients randomised to PAC arm in each study centre with a standard ECG-gated protocol. CCT studies performed at the coordinating centre and in all the other participating centres will be analysed at the core lab by at least two of three radiologists proficient

in cardiac imaging (AD, CG and PF) using a dedicated workstation (Advantage Workstation VolumeShare V.4.7, GE Healthcare) with coronary analysis software (CardIQ3 Package, GE Healthcare).

Coronary analysis at the participating centres will be performed using dedicated software provided by the vendor of the scanner (eg, IntelliSpace Portal, Philips Healthcare; syngo.CT Coronary Analysis, Siemens Healthineers; Vitrea Advanced Visualisation CT SURE-Plaque, Canon Medical Systems), using vendor neutral software (such as Circle cvi42, Circle Cardiovascular Imaging) or using PACS plug-ins (Synapse Cardiovascular 5.0, Fujifilm, eg) depending on the local radiologist usual workflow.

All coronary artery branches will be reconstructed and analysed. ISR on ULM will be assessed.

Percutaneous coronary intervention

Index CA and PCI of ULMCA will be performed according to local protocols and recommendation of ESC guidelines on myocardial revascularisation.¹ The choice of stenting technique (provisional versus 2-stent technique) both at the index procedure and during follow-up will be left at operating physicians' discretion. The use of intracoronary imaging (IVUS or optical coherence tomography (OCT)) to optimise stent deployment and check the optimal result of PCI and the use of invasive physiological assessment (FFR or instantaneous waves free ratio (iFR)) to confirm the haemodynamic relevance of stenoses and ISR <50% of ULM diameter will be strongly encouraged but will be left at operators' choice.

Optimal medical therapy

Dual antiplatelet therapy with acetylsalicylic acid and thienopyridines should be given in all cases, with preloading and the post-PCI duration based on the patient's risk of bleeding and European guidelines recommendations.¹ Each site is provided with a standard operating procedure for delivering and monitoring optical medical therapy (OMT), which sets out classes of drugs appropriate for trial patients regard to secondary prevention of atherosclerosis as well as recommended treatment targets including lipid profile, HbA1c, blood pressure and heart rate. Researchers performing enrolment and randomisation will be actively involved to ensure that patients in both arms of the trial receive OMT.

Trial organisation

Trial registration (NCT04144881) was completed after recruitment commenced. The first patient was randomised on 11 October 2019, and, at the time of this publication, 15 patients have been randomised. There have been no major amendments to the protocol. Between the approval of this protocol and the first patient enrolment updated versions of ESC guidelines on myocardial revascularisation, ST-elevation MI management and recommendations on target goals for secondary prevention of atherosclerotic disease have been published. Clinical

management of patients enrolled in this trial will anyway follow the most updated indications of ESC.

DISCUSSION

Given the undefined picture surrounding the appropriateness of PAC following PCI of the ULMCA with DES-II, aim of this trial is to evaluate, in a prospective, randomised, setting, the potential benefits of a PAC-based strategy versus an ischaemia-driven and symptoms-driven conservative management. Disease of the native ULMCA is associated with an unfavourable prognostic outcome, which can be at least partially reversed by revascularisation. Significant stenosis of the stented ULM caused by ISR, however, presents some peculiar pathophysiological, flow-related and shear-stress features, which partly makes it a distinct disease as compared with native vessel atherosclerosis. Treatment of ISR, moreover, is a scarcely standardised and often complex procedure; some uncertainties persist regarding the best strategy to treat ISR (stent-in-stent, drug-eluting balloons, dilation with conventional balloons).⁶ CCT can precisely and not-invasively assess the presence of ISR in the stented ULM, without exposing the patients to the risks of invasive catheterisation.¹² CCT may provide an accurate reconstruction of the stented vessels, exposing the patients to a limited amount of contrast dye (approximately, 80–100 cc) and of radiation dose (approximately, 92 mGy). CCT has a very high negative predictive value for ISR, thus limiting the negative impact of the indiscriminate execution of invasive angiography to all patients treated by PCI of the ULM. Only patients with relevant ISR of ULM at CCT will undergo coronary angiography to confirm the presence of critical stenosis, and FFR/iFR and/or IVUS/OCT will be performed in dubious cases. An increased rate of PCI must be taken in to account with a PAC-based approach.⁷ However, with the accurate, stepwise selection of the patients and the lesions amenable to PCI of our study protocol, based on CCT, coronary angiography and, where necessary, IVUS/OCT or FFR/iFR, the increased rate of PCI is not expected to bear a negative prognostic impact. Based on these premises, our hypothesis is that early, appropriate, detection of ULM ISR and its subsequent treatment may positively impact patients' survival and reduce the incidence of adverse cardiovascular events.

Significance and innovations

The present proposal has at least four points of innovations

1. The translation of the concept of PAC from an invasive procedure requiring hospitalisation to a non-invasive procedure which can be performed as a routine ambulatory examination.
2. The demonstration of accuracy of CCT to detect ISR in a high-risk setting like patients with stented ULMCA.
3. To focus resources only to high-risk patients with a non-invasive technique, which presents lower direct and indirect costs (ie, no need for hospitalisation) as compared with invasive angiography.

4. The benefit for the patients who will be treated in a non-advanced phase of progression of the coronary artery disease.

Possible limitations

A possible drop-out of patients from the study for different reasons is expected (informed consent retrieval, lost to follow-up). For this reason, the sample size calculation accounted for a 10% patients' drop-out. A significant early prognostic benefit of the PAC strategy over conservative management can be hypothesised; for this reason a 18 months interim analysis with safety purposes will be conducted to exclude a significant early advantage (or disadvantage) of the PAC strategy. Finally, this trial will try to address a potential issue related to a low diagnostic resolution of CCT for the presence of ISR, with false negative diagnosis of absence of ISR.

Conclusion

The PULSE trial is designed to assess in a prospective, randomised and controlled setting the role of a non-invasive PAC strategy performed with computed coronary tomography versus a conservative symptoms and ischaemia-driven management, in patients treated with percutaneous revascularisation on ULMCA. The trial will also give the opportunity to evaluate the performance of CCT as an early, non-invasive diagnostic tool to detect ISR of left main artery. Early detection and treatment of ISR on ULM is awaited to significantly reduce the incidence of adverse outcome events in patients treated with PCI on such vessel.

ETHICS AND DISSEMINATION

The trial is carried out in accordance with the declaration of Helsinki and in keeping with Good Clinical Practice Guidelines. All participants will be asked to provide informed consent to be involved and their general practitioners will be made aware about the enrolment and trial protocol through a dedicated personal letter. Trial results will be published in peer-reviewed scientific journals and presented at national and international conferences relevant to cardiovascular care and internal academic seminars.

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Contributors FD, GCo conceived the study idea, led the funding application and protocol development. ODF, FA, LZ, LG and LF contributed to protocol drafting and development and coordinated ethical approval process. MB and EC contributed to protocol development and supported FD and GCo with development of the study database, and plans for quantitative data management and statistical analysis. GM, FV, MT contributed to protocol development and provided expert cardiovascular advice about clinical management and follow-up planning. GM led the coordinating centre. PF contributed to protocol development and provided expert radiology advice as lead of radiology unit of coordinating centre. MI, MG, GQ, AG, RG, GB, VG, AS contributed to protocol development and provided expert advice about revascularisation procedures and techniques. AD, DT, CG, FS, PV and GCa contributed to protocol development and provided advices about CCT devices, software and image acquisitions. AV and FM contributed to the revised version of the protocol and the revised draft of this manuscript, provided advices about CCT devices, software and image acquisition. All authors have read and approved the final version of the manuscript.

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