International Journal of Cardiology 292 (2019) 253–257

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Design of CTP-PRO study (impact of stress Cardiac computed Tomography myocardial Perfusion on downstream resources and PROgnosis in patients with suspected or known coronary artery disease: A multicenter international study)

Gianluca Pontone [a,*,1], Carlo De Cecco [b,1], Andrea Baggiano [a], Andrea I. Guaricci [c], Marco Guglielmo [a], Tim Leiner [d], Joao Lima [e], Pál Maurovich-Horvat [f], Giuseppe Muscogiuri [a], John W. Nance [g], U. Joseph Schoepf [g]

[a] Centro Cardiologico Monzino, IRCCS, Milan, Italy
[b] Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA, USA
[c] Institute of Cardiovascular Disease, Department of Emergency and Organ Transplantation, University Hospital Policlinico, Bari, Italy
[d] Department of Radiology, Utrecht University Medical Center, Utrecht, the Netherlands
[e] The Johns Hopkins Hospital, Baltimore, USA
[f] MTA-SE Cardiovascular Imaging Research Group (CIRG) Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[g] Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

ARTICLE INFO

Article history:
Received 24 December 2018
Received in revised form 5 June 2019
Accepted 6 June 2019
Available online 12 June 2019

Keywords:
Coronary artery disease
Cardiac computed tomography angiography
Computed tomography perfusion
Non-invasive test
Invasive coronary angiography
Major adverse cardiac events

ABSTRACT

Background: CT myocardial perfusion imaging (CTP) represents one of the newly developed CT-based techniques but its cost-effectiveness in the clinical pathway is undefined. The aim of the study is to evaluate the usefulness of combined evaluation of coronary anatomy and myocardial perfusion in intermediate to high-risk patients for suspected CAD or with known disease in terms of clinical decision-making, resource utilization and outcomes in a broad variety of geographic areas and patient subgroups.

Methods: CTP-PRO study is a cooperative, international, multicentre, prospective, open-label, randomized controlled study evaluating the cost-effectiveness of a CCTA+CTP strategy (Group A) versus usual care (Group B) in intermediate-high risk patients with suspected or known CAD who undergo clinically indicated diagnostic evaluation. A total sample size of 2000 subjects will be enrolled and followed up for 24 months. The primary endpoint is the reclassification rate of CCTA in group A due to the addition of CTP. The secondary endpoint will be the comparison between groups in terms of non-invasive and invasive downstream testing, prevalence of obstructive CAD at ICA, revascularization, cumulative ED and overall cost during the follow-up at 1- and 2-years. The tertiary endpoint will be the comparison between each group in terms of MACE and cost-effectiveness at 1- and 2-years.

Conclusions: The study will provide information to patients, health care providers and other stakeholders about which strategy could be more effective in the diagnosis of suspected CAD in intermediate to high-risk patients or in the symptomatic patients with known CAD and previous history of revascularization.

1. Introduction

Coronary CT angiography (CCTA) is expanding its role as a powerful non-invasive tool for the evaluation of suspected coronary artery disease (CAD) [1]. However, a pure anatomical approach is inadequate to predict hemodynamic relevance of coronary stenoses, and improved outcomes have been observed among patients undergoing a functional test [2,3]. The use of CCTA is usually suggested in low to intermediate risk for its diagnostic and prognostic role to rule out CAD with low radiation exposure [4–7]. In the setting of intermediate to high risk patients, the addition of functional information is prognostically useful [8] and, in patients with previous history of percutaneous coronary intervention

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CCTA, computed tomography angiography; CIN, contrast injury nephropathy; CMR, cardiac magnetic resonance; CTP, computed tomography perfusion; ED, effective dose; ICA, invasive coronary angiography; ISR, intra-stent restenosis; MACE, major adverse cardiac events; MBF, myocardial blood flow; MI, myocardial infarction; NIT, non-invasive test; PCI, percutaneous coronary intervention; PET, positron emission tomography; SCCT, society of cardiovascular computed tomography; SPECT, single photon emission computed tomography.

* Corresponding author at: Via C. Parea 4, 20138 Milan, Italy.
E-mail address: gianluca.pontone@ccfm.it (G. Pontone).

[1] Pontone G and De Cecco C provided equal contribution.

https://doi.org/10.1016/j.ijcard.2019.06.012
0167-5273/

(PCI), functional strategy has been shown to be more cost-effective as compared to anatomical assessment [9]. CT myocardial perfusion imaging (CTP) represents one of the newly developed CT-based techniques [10], combining both anatomical and functional evaluation of CAD in a single imaging modality [11,12]. CTP was also compared to the gold standard of invasive fractional flow reserve (FFR), showing a sensitivity and specificity in detecting flow-limiting coronary stenosis of 88% and 80%, respectively [11]. More recently, stress CTP was shown to provide additional diagnostic value as compared to CCTA alone in intermediate to high risk patients [13,14]. The purpose of this study will be to evaluate the usefulness and impact of combined evaluation of coronary artery anatomy and myocardial perfusion with CCTA+CTP in intermediate to high risk patients for suspected CAD or with known disease in terms of clinical decision-making, resource utilization, and outcomes in a broad variety of geographic areas and patient subgroups.

2. Methods

CTP-PRO study is a cooperative, international, multicentre, prospective, open-label, randomized controlled study evaluating the cost-effectiveness of a CCTA+CTP strategy versus usual care in intermediate to high risk patients with suspected or known CAD who undergo clinically indicated diagnostic evaluation.

2.1. Inclusion and exclusion criteria

Consecutive patients with known or suspected CAD referred for clinically indicated diagnostic evaluation will be included. CCTA has to be performed with the state of art in terms of scanner technology as follows: Revolution CT (GE Healthcare, Milwaukee, WI), CardioGraphe (GE Healthcare, Milwaukee, WI), SOMATOM Definition Flash or Force (Siemens, Forchheim, Germany), Brilliance iCT and IQon CT (Philips, Best, Netherlands), Aquilion One Vision (Canon Medical Systems Corp., Otawara, Japan). All inclusion and exclusion criteria are listed in Table 1. Each enrolling centre will fill a logbook file with all the screened subjects, specifying reasons for inclusion or exclusion from the study. The study workflow is shown in Fig. 1.

2.2. Screening procedure and enrollment

Patients will be screened for study eligibility by site personnel. Patients meeting all selection criteria will be asked to sign an informed consent document prior to undergoing any study-specific evaluation. After all inclusion and exclusion criteria will be met and the informed consent document signed, a structured interview will be performed and a clinical history obtained, assessing the presence of common cardiac risk factors, drug therapy (focus on statin, aspirin and/or antiplatelet agent use) and symptoms (typical or atypical angina, as previously described, to estimate the pre-test likelihood of CAD) [15].

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Consecutive patients (age ≥ 18 years) with known or suspected CAD referred for clinically indicated diagnostic evaluation will be included in this study. As additional inclusion criteria the CCTA has to be performed with the state of art in terms of scanner technology as follow: Revolution CT (GE Healthcare, Milwaukee, WI), CardioGraphe (Arineta, Caesarea, Israel), SOMATOM Force (Siemens, Forchheim, Germany), Brilliance iCT and IQon CT (Philips, Best, Netherlands), Aquilion One Vision (Toshiba Medical Systems Corp., Otawara, Japan).
Exclusion criteria
▪ Performance of any non-invasive diagnostic testing within 90 days before enrollment
▪ Low to intermediate pre-test likelihood of CAD according to the updated Diamond-Forrester risk model score
▪ Acute coronary syndrome
▪ Need for an emergent procedure
▪ Evidence of clinical instability
▪ Contra-indication to contrast agent administration and/or impaired renal function
▪ Inability to sustain a breath hold
▪ Pregnancy
▪ Cardiac arrhythmias
▪ Presence of pace maker or implantable cardioverter defibrillator
▪ Contra-indications to the administration of sub-lingual nitrates, beta-blockade and adenosine
▪ Structural cardiomyopathy outside of suspected or know ischemic heart disease

2.3. Randomization procedure for all patients

Upon completion of the screening procedure and enrollment, the patients will be randomized 1:1 to the CT-based strategy (Group A) or usual care (Group B).

2.4. Patient preparation for patients in Group A

Patients will be asked to refrain from smoking and caffeine for 24 h and to maintain fasting for 6 h before the scan. All patients will be monitored with continuous blood pressure measurement and ECG to evaluate mean heart rate (HR) and HR variability (HRv) during a breath hold test as previously described [16]. For all patients with a resting HR > 65 bpm before the scan, β-blockade should be administered to achieve a target HR ≤ 65 bpm. No exclusion criteria will be adopted in terms of maximum HR thanks to the new scanner technology that will be used in the study. Before the rest scan, all patients will receive sublingual nitrates to ensure coronary vasodilatation.

2.5. Rest CCTA performance and interpretation for patients Group A

CCTA will be performed with one of the latest generation scanners mentioned above and in agreement with the recommendations of the Society of Cardiovascular Computed Tomography (SCCT) [17]. Scan parameters, contrast agent type and protocol injection will be in agreement with on-site practice. CCTA datasets will be transferred to a dedicated image-processing workstation and undergo on-site evaluation according to the SCCT guidelines for reporting [17]. For analysis, coronary arteries will be segmented according to a 16 segment model [18]. The causes of impaired image quality will be classified as blooming artifacts generated by large calcifications, motion artifacts related to non-compliance with breath holding, misalignment of sections related to variation of HR, or impaired signal- or image-to-noise ratio. Accordingly, 4-point image quality score (Likert score) will be used to estimate the image quality. In each coronary artery, coronary atherosclerosis will be defined as the presence of any tissue structures larger than 1 mm^2 either within the coronary artery lumen or adjacent to it that can be discriminated from the surrounding pericardial tissue, epicardial fat, or vessel lumen itself. All detected plaques will be classified as non-calcified plaque, mixed plaque, or calcified plaque [7]. All calcified plaques will be further classified as mild calcification (arc <90°), moderate calcification (arc: 90–179°), and severe calcification (arc >179°) in a cross-sectional view of the coronary vessel [7]. The severity of coronary lesions will be quantified in multi-planar curved reformatted images by identifying the minimum diameter and reference diameter for all stenosis, and the percentage of stenosis will be derived according to the following formula: (Dref - Dmin)/Dref · 100, where Dref is the reference diameter (mean of diameters of coronary artery segments free by disease immediately before and after the stenosis) and Dmin is the minimum diameter. Then, luminal diameter stenosis will be quantified as none (0% luminal stenosis), very mild (1% to 29% luminal stenosis), mild (30% to 50% luminal stenosis), moderate (51% to 70% luminal stenosis), obstructive (71% to 90% luminal stenosis), sub-totally occluded (91% to 99% luminal stenosis), occluded (100% luminal stenosis), or non-evaluable. A stenosis >50% will be considered as significant from an anatomical point of view. For coronary artery segments with stents, degree of intrastent restenosis (ISR) will be evaluated by visual assessment of intraluminal contrast density. Contrast attenuation will be measured in Hounsfield units and compared with short- and long-axis views inside and outside the stented segment. Stent narrowing will be graded from 0 to 3 (grade 0, patent lumen with no visible ISR; grade 1, non-obstructive ISR with <50% lumen narrowing for a patent stent with a hypoattenuating rim between the metallic struts and the enhanced lumen; grade 2, obstructive ISR with >50% lumen narrowing for stent lumen appearance, and grade 3, total occlusion for a stent lumen with lower attenuation than the contrast-enhanced vessel proximal to the stent and no visualized runoff distal to the stent) [19]. ISR > 50% will be considered as significant from an anatomical point of view.

For CABG, each graft will be visually evaluated and scored as patent, non-significant stenosis ≤50%, significant stenosis >50%, or occluded.

2.6. Randomization procedure for patients in Group A

Upon completion of rest CCTA, patients with negative CCTA will follow the usual standard of care. For patients with positive CCTA results, additional stress CTP will be performed subsequently. The decision to perform static stress CTP or dynamic stress CTP will be based on local practice and technology. The referring physicians will use the information given by the test result according to specific clinical guidelines and to local practice (optimal medical therapy prescription, further non-invasive or invasive tests).

2.7. Stress CTP performance and interpretation

Vasodilatation will be induced with i.v. adenosine injection or regadenoson based on local practice.

For static stress CTP, at the end of stressor infusion, a single data sample will be acquired during first-pass enhancement according to local practice and scan protocol provided by each vendor (see supplemental material for details of the scan protocol for each vendor). Datasets of static stress CTP will be transferred to a dedicated image-

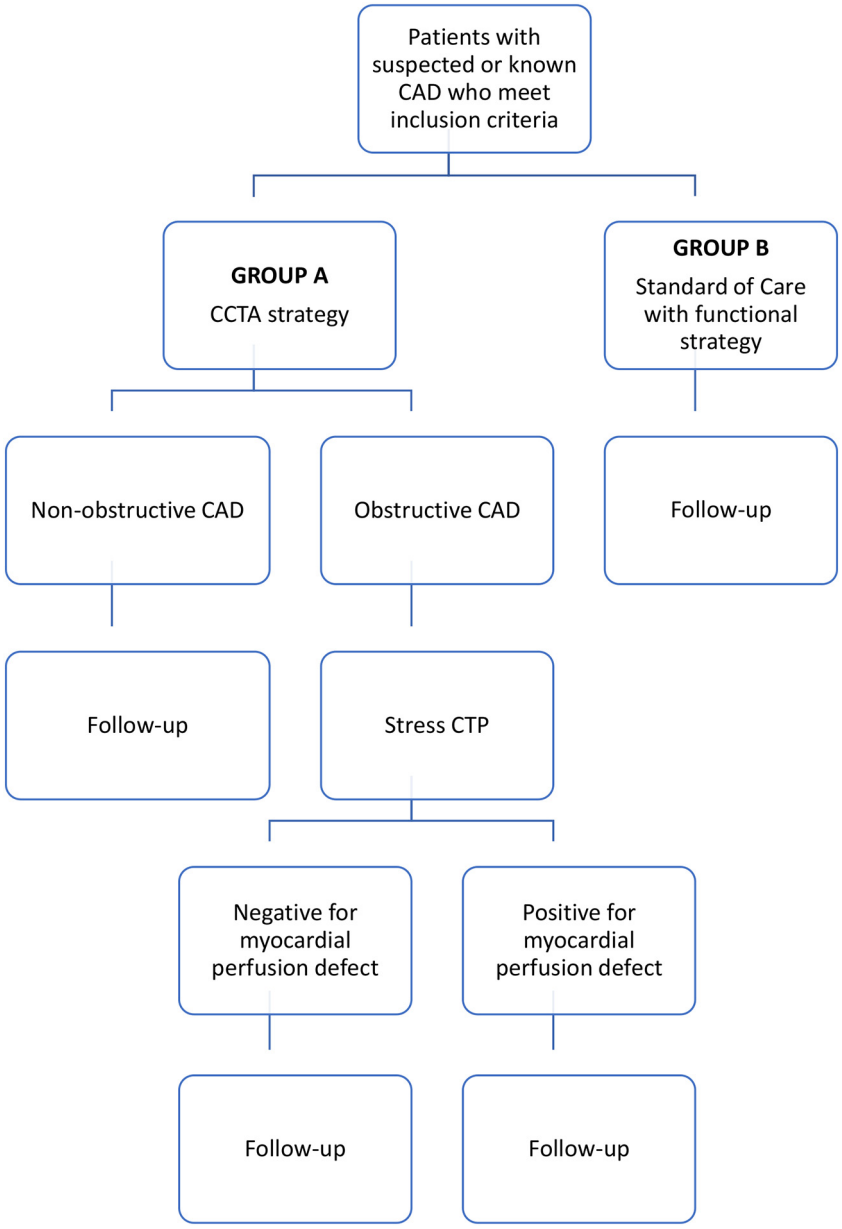

Fig. 1. Study workflow. CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CTP: computed tomography perfusion.

processing workstation. The evaluation will be performed on a short axis (apical, medium and basal slices) and long-axis view (2-, 3- and 4-chamber projections) with 8-mm thick average multiplanar reformatted images [20]. A narrow window width and level (350 W and 150 L) will be used for perfusion defect evaluation. Each myocardial segment will be correlated as previously described by Cerci et al. [21]. The adjudication process will be applied between a significant CAD and at least 1 myocardial perfusion defect in primary or secondary territories.

As a first step, a 4-point image quality score will be given for each myocardial segment regarding the diagnostic confidence of perfusion defect evaluation, based on image quality [22]. True perfusion defects will be defined as subendocardial hypoattenuation encompassing ≥25% of transmural thickness within a specific coronary territory.

For dynamic CTP, vasodilatation will be induced with the same protocol described for static stress CTP. Under pharmacological stress, multiple sequential samples of myocardial attenuation will be acquired according to the local practice and scan protocol provided by each vendor (see supplemental material for details of the scan protocol for each vendor).

Datasets of dynamic stress CTP will be evaluated by on-site dedicated software. The evaluation will be performed on a short axis (apical, medium and basal slices) with 8-mm thick average multiplanar reformatted images and a narrow window width and level (350 W and 150 L) will be used for perfusion defect evaluation. Each myocardial segment will be correlated as previously described [21].

As a first step, a 4-point image quality score is given for each myocardial segment as previously described for static stress CTP. True perfusion defects will be quantitatively defined according to vendor-specific software, and myocardial blood flow (MBF) values provided.

For all patients with previous history of MI the presence of reversible ischemia will be obtained by the comparison between rest and stress perfusion. A further late acquisition to detect scar according to the local protocol is recommended but not mandatory.

2.8. Radiation exposure estimation

The effective radiation dose (ED) will be calculated as the product between dose–length product and a conversion coefficient for the chest ($K = 0.014$ mSv/(mGy*cm) [23]. For other tests the ED reported in the report or the mean ED available in the literature for that specific test will be used.

2.9. Reclassification rate in patient management

The reclassification rate in patient management will be evaluated between CCTA alone versus both CCTA and CTP when available. The reclassification rate of management plans will be assessed by a blinded independent review committee and local physician teams separately. In detail, for each enrolled patient in whom both CCTA and stress CTP will be performed, the endpoint review committee will use data from coronary CTA and CTP, along with the clinical data to determine the management plan using the following criteria: (a) optimal medical therapy, (b) more non-invasive information required,

(c) invasive evaluation required, (d) revascularization treatment (PCI or CABG or hybrid treatment).

2.10. Management for patients in Group B

Patients randomized to this group will be evaluated according to current clinical guidelines [4] with the following approaches: (a) functional non-invasive tests (stress ECG, or imaging-based tests such as Stress Echo, Stress CMR, SPECT or PET) as a gatekeeper for ICA; (b) direct referral to ICA.

2.11. Follow-up

Patient follow-up will be performed at 1 year (± 1 month) and 2 years (± 1 month) by trained interviewers who check medical records or by phone interview collecting the following information:

1. Downstream testing. The results of the index test will be provided to the reference cardiologist of the patients' institution who will make clinical decisions based on the integrated evaluation of patient clinical assessment and index test findings. The following downstream testing will be recorded from study entry until the end of follow-up: [1] NITs: non-invasive diagnostic tests, including further CCTA or stress testing (exercise or pharmacological stress), with detection of ischemia by ECG, myocardial perfusion, or wall motion abnormalities; and [2] number of ICA and prevalence of obstructive CAD at ICA.
2. Overall radiation exposure. We will measure the cumulative ED over the entire study period by assessing the original average dose for each test performed during the follow-up. In case the ED for each test is not known, we will use the standard ED available for each test in the literature.
3. Outcomes. Events will be defined according to the following definitions: a) hospitalization for cardiac reason; b) revascularization by PCI or CABG; c) unstable angina; d) non-fatal MI; e) cardiac death: any death because of immediate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia) or vascular cause (e.g., cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause). Unwitnessed death and death of unknown cause will be classified as cardiovascular death. MACE will be defined as a combined endpoint of unstable angina, nonfatal MI, and cardiac death. An independent clinical events adjudication committee will review the agreement between all events and the provided definitions.
4. Cost-effectiveness estimation: The cost of different medical care strategies will be measured with a bottom-up estimation by multiplying counts of resource use by standardized cost weights that will be calculated according to local reimbursement [24] [25]. For the purpose of this analysis, we will include all costs between study entry and 2-year follow-up, including the cost of the index study test. In order to adjust for differences among patient groups, we will develop a propensity score for use of usual care instead of cCTA, and a second propensity score for use of cCTA+CTP instead of cCTA. We will develop these two propensity score models using multivariable logistic regression, based only on patients enrolled in centres that perform all tests of interest, using baseline clinical characteristics that will be recorded on study data forms [26]. For each patient, the projected remaining life expectancy will be calculated using the observed survival time of patients who died and their projected life expectancy (based on the age-sex matched Italian population) to estimate life-years lost. We will assign 2 life-years lost to every patient who experiences a MI and survives for the remaining follow-up time [9]. Finally, the cost-effectiveness ratio will be calculated according to the following equation: (Index test cost + downstream diagnostic tests cost) / projected remaining life expectancy.

2.12. Endpoints of the study

The primary endpoint of the study is the reclassification rate of CCTA in group A due to the addition of CTP according to the following algorithm: A) non-obstructive CAD with negative matched functional evaluation was considered negative; B) non-obstructive CAD with positive matched functional evaluation was considered still negative; C) obstructive CAD with negative matched functional evaluation was considered negative; and D) obstructive CAD with positive matched functional evaluation was deemed positive.

The secondary endpoint will be the comparison between group A and group B in terms of non-invasive and invasive downstream testing, prevalence of obstructive CAD at ICA, revascularization, cumulative ED and overall cost during the follow-up at 1- and 2-years. The tertiary endpoint will be the comparison between each group in terms of MACE and cost-effectiveness at 1- and 2-years.

2.13. Statistical analysis

The sample size is defined based on the primary endpoint. Based on previous data [9,13,27] and assuming a prevalence of obstructive CAD of 55%, a rate of CTP positive for perfusion defect among patients with obstructive CAD of 30% and a conservative rate of reclassification of patients' management by integration of CTP with CCTA of 10%, 473 patients with positive CCTA should be enrolled corresponding to an overall population for the CCTA arm of 860 patients. Considering a drop-off up to 10%, the final overall population should be of 1912 patients. This sample size should ensure >90% power to determine the effect of CTP on reclassification rate of CAD management. Discrete variables will be presented as absolute number or percentage while continuous data will be presented as mean ± SD or medians with the range between first and third quartile. Groups will be compared by independent sample Student *t*-test or Mann-Whitney *U* test for continuous variables and by chi-square or Fisher exact test for categorical variables. The event free survival probability will be estimated by Kaplan-Meier survival analysis and log-rank statistic. A Cox proportional hazards model will be employed to estimate the relative hazard of events by the different test strategies, thus deriving hazard ratios and 95% confidence intervals. A 2-sided p value of <0.05 was considered statistically significant.

3. Discussion

CCTA has proven itself as a robust technique in terms of diagnosis [28] and prognostic stratification [8,29] with low radiation exposure [30]. Some studies comparing the cost-effectiveness of an anatomical strategy versus standard of care in these settings have shown a superiority of usual practice. Hlatky et al. [26] in an observational prospective registry of 1703 patients with suspected CAD showed that functional strategy with SPECT was associated with a 15% and 22% lower cost as compared with CCTA ($p < 0.01$) or positron emission tomography ($p < 0.0001$), respectively, with a comparable number of major adverse cardiac events (1.6% versus 0.7% versus 5.5%, respectively). Douglas et al. [31] showed that CCTA, as compared with a functional strategy approach, is associated with a lower rate of non-obstructive CAD at ICA evaluation (3.4% versus 4.3%; p 0.02) at the cost of a trend of higher number of patients referred to catheterization (12.2% versus 8.0%) and revascularization procedures (6.2% versus 3.2%), and higher cumulative ED (12 mSv versus 10.1 mSv; $p < 0.001$) without any improvement in the clinical outcomes. Mudrick et al. [32] showed a higher rate of further non-invasive testing (10% versus 3%), catheterization (26% versus 15%), and revascularization procedures (13% versus 8%) within 90 days from CCTA. Further, in a setting of revascularized patients, Pontone et al. [9] showed that compared with a functional strategy based on stress cardiac magnetic resonance (CMR), CCTA was associated with a higher rate of subsequent non-invasive tests (28% versus 17%; p 0.0009), ICA (31% versus 20%; p 0.0009), and revascularization procedures (24% versus 16%; p 0.007). Moreover, patients undergoing stress-CMR showed a lower rate of MACE (5% versus 10%; $p < 0.010$) and cost-effectiveness ratio (119.98 ± 250.92 versus 218.12 ± 298.45 Euro/y; $p < 0.001$).

More recently, the addition of stress-CTP to CCTA was shown to significantly improve overall diagnostic accuracy of CCTA alone when compared to ICA plus FFR in the setting of intermediate to high risk patients [13,14]. However, comparative data of cost-effectiveness of a combined anatomical plus functional strategy with CCTA plus CTP versus the usual care pathway or CCTA alone strategy are unknown.

In conclusion, the CTP-PRO study will provide information about which strategy could be more effective in the diagnosis of suspected CAD in intermediate to high risk patients or in the symptomatic patients with known CAD and previous history of revascularization.

3.1. Status of the study

The study is registered at ClinicalTrials.gov with the Protocol Number NCT03976921.

Initially, 4 coordinating sites will contribute data. Data collection activities will begin with the aim to collect data on approximately 2000 patients. Participating sites represent academic university-based medical centers. The anticipated duration of the study will be approximately 12 months for enrollment, 24 months for follow-up, and 4 months for data analysis. Total study duration including follow-up and data analysis is expected to be approximately 40 months. The first enrollment is planned for June 2019.

Declaration of Competing Interest

G. Pontone declares institutional fee of institutional research grant from GE Healthcare, Bracco, Bayer, Medtronic, HeartFlow.

U.J. Schoepf has received institutional research support and/or personal fees from Astellas, Bayer, Elucid Bioimaging, GE Healthcare, Guerbet, HeartFlow, Inc., and Siemens Healthcare.

C.N. De Cecco receives institutional research support from Siemens and Bayer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.012.

References

[1] M.J. Budoff, D. Dowe, J.G. Jollis, et al., Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial, J. Am. Coll. Cardiol. 52 (2008) 1724–1732.

[2] N.H. Pijls, W.F. Fearon, P.A. Tonino, et al., Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study, J. Am. Coll. Cardiol. 56 (2010) 177–184.

[3] L.J. Shaw, D.S. Berman, D.J. Maron, et al., Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy, Circulation 117 (2008) 1283–1291.

[4] Montalescot G, Sechtem U, Achenbach S et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. European heart journal 2013;34:2949–3003.

[5] Pontone G, Muscogiuri G, Baggiano A et al. Image quality, overall evaluability, and effective radiation dose of coronary computed tomography angiography with prospective electrocardiographic triggering plus intracycle motion correction algorithm in patients with a heart rate over 65 beats per minute. J. Thorac. Imaging 2018;33: 225–231.

[6] F. Erthal, M. Premaratne, Y. Yam, et al., Appropriate use criteria for cardiac computed tomography: does computed tomography have incremental value in all appropriate use criteria categories, J. Thorac. Imaging 33 (2018) 132–137.

[7] G. Pontone, E. Bertella, S. Mushtaq, et al., Coronary artery disease: diagnostic accuracy of CT coronary angiography—a comparison of high and standard spatial resolution scanning, Radiology 271 (2014) 688–694.

[8] G. Pontone, D. Andreini, A.L. Bartorelli, et al., A long-term prognostic value of CT angiography and exercise ECG in patients with suspected CAD, J. Am. Coll. Cardiol. Img. 6 (2013) 641–650.

[9] G. Pontone, D. Andreini, A.I. Guaricci, et al., The STRATEGY study (Stress Cardiac Magnetic Resonance Versus Computed Tomography Coronary Angiography for the Management of Symptomatic Revascularized Patients): resources and outcomes impact, Circ. Cardiovasc. Imaging 9 (2016).

[10] J.D. Schuijf, W. Wijns, J.W. Jukema, et al., Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging, J. Am. Coll. Cardiol. 48 (2006) 2508–2514.

[11] R.A. Takx, B.A. Blomberg, H. El Aidi, et al., Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis, Circ. Cardiovasc. Imaging 8 (2015).

[12] Z. Yang, H. Zheng, T. Zhou, et al., Diagnostic performance of myocardial perfusion imaging with SPECT, CT and MR compared to fractional flow reserve as reference standard, Int. J. Cardiol. 190 (2015) 103–105.

[13] Pontone G, Andreini D, Guaricci AI et al. Incremental diagnostic value of stress computed tomography myocardial perfusion with whole-heart coverage CT scanner in intermediate- to high-risk symptomatic patients suspected of coronary artery disease. J. Am. Coll. Cardiol. Img. 2018.

[14] G. Pontone, D. Andreini, A.I. Guaricci, et al., Quantitative vs. qualitative evaluation of static stress computed tomography perfusion to detect haemodynamically significant coronary artery disease, Eur. Heart J. Cardiovasc. Imaging 19 (11) (2018) 1244–1252.

[15] J.M. Jensen, M. Voss, V.B. Hansen, et al., Risk stratification of patients suspected of coronary artery disease: comparison of five different models, Atherosclerosis 220 (2012) 557–562.

[16] G. Pontone, D. Andreini, E. Bertella, et al., Impact of an intra-cycle motion correction algorithm on overall evaluability and diagnostic accuracy of computed tomography coronary angiography, Eur. Radiol. 26 (2016) 147–156.

[17] J. Leipsic, S. Abbara, S. Achenbach, et al., SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee, J. Cardiovasc. Comput. Tomogr. 8 (2014) 342–358.

[18] W.G. Austen, J.E. Edwards, R.L. Frye, et al., A reporting system on patients evaluated for coronary artery disease. Report of the ad hoc committee for grading of coronary artery disease, council on cardiovascular surgery, American Heart Association, Circulation 51 (1975) 5–40.

[19] D. Andreini, G. Pontone, A.L. Bartorelli, et al., Comparison of feasibility and diagnostic accuracy of 64-slice multidetector computed tomographic coronary angiography versus invasive coronary angiography versus intravascular ultrasound for evaluation of in-stent restenosis, Am. J. Cardiol. 103 (2009) 1349–1358.

[20] R.C. Cury, T.A. Magalhaes, A.T. Paladino, et al., Dipyridamole stress and rest transmural myocardial perfusion ratio evaluation by 64 detector-row computed tomography, J. Cardiovasc. Comput. Tomogr. 5 (2011) 443–448.

[21] R.J. Cerci, A. Arbab-Zadeh, R.T. George, et al., Aligning coronary anatomy and myocardial perfusion territories: an algorithm for the CORE320 multicenter study, Circ. Cardiovasc. Imaging 5 (2012) 587–595.

[22] G. Feuchtner, R. Goetti, A. Plass, et al., Adenosine stress high-pitch 128-slice dual-source myocardial computed tomography perfusion for imaging of reversible myocardial ischemia: comparison with magnetic resonance imaging, Circ. Cardiovasc. Imaging 4 (2011) 540–549.

[23] A.J. Einstein, K.W. Moser, R.C. Thompson, M.D. Cerqueira, M.J. Henzlova, Radiation dose to patients from cardiac diagnostic imaging, Circulation 116 (2007) 1290–1305.

[24] K. Moschetti, D. Favre, C. Pinget, et al., Comparative cost-effectiveness analyses of cardiovascular magnetic resonance and coronary angiography combined with fractional flow reserve for the diagnosis of coronary artery disease, J Cardiovasc Magn Reson 16 (2014) 13.

[25] G. Turchetti, V. Lorenzoni, S. Bellelli, et al., Effectiveness and costs of different strategies for the diagnosis of stable coronary artery disease results from the evinci study. Value in health: the journal of the international society for, Pharmacoeconomics and Outcomes Research 17 (2014) A474.

[26] M.A. Hlatky, D. Shilane, R. Hachamovitch, M.F. Dicarli, Economic outcomes in the study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease registry: the SPARC study, J. Am. Coll. Cardiol. 63 (2014) 1002–1008.

[27] M. Lubbers, A. Coenen, M. Kofflard, et al., Comprehensive cardiac CT with myocardial perfusion imaging versus functional testing in suspected coronary artery disease: the multicenter, randomized CRESCENT-II trial, J. Am. Coll. Cardiol. Img. 11 (11) (2017) 1625–1636.

[28] D.B. Mark, D.S. Berman, M.J. Budoff, et al., ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on expert consensus documents, Circulation 121 (2010) 2509–2543.

[29] J.K. Min, A. Dunning, F.Y. Lin, et al., Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the international multicenter CONFIRM (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry) of 23,854 patients without known coronary artery disease, J. Am. Coll. Cardiol. 58 (2011) 849–860.

[30] G. Pontone, D. Andreini, A.L. Bartorelli, et al., Diagnostic accuracy of coronary computed tomography angiography: a comparison between prospective and retrospective electrocardiogram triggering, J. Am. Coll. Cardiol. 54 (2009) 346–355.

[31] P.S. Douglas, U. Hoffmann, Anatomical versus functional testing for coronary artery disease, N. Engl. J. Med. 373 (2015) 91.

[32] D. Mudrick, L.A. Kaltenbach, B. Shah, et al., Downstream testing and subsequent procedures after coronary computed tomographic angiography following coronary stenting in patients >/=65 years of age, Am. J. Cardiol. 110 (2012) 776–783.