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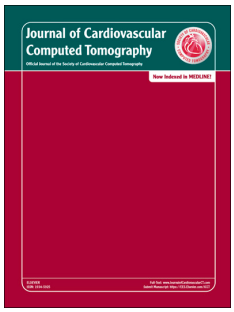

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PII: S1934-5925(18)30207-7

DOI: 10.1016/j.jcct.2018.06.003

Reference: JCCT 1117

To appear in: *Journal of Cardiovascular Computed Tomograph*

Received Date: 25 April 2018

Revised Date: 4 May 2018

Accepted Date: 15 June 2018

Please cite this article as: Andreini D, Mushtaq S, Pontone G, Conte E, Sonck J, Collet C, Guglielmo M, Baggiano A, Trabattoni D, Galli S, Montorsi P, Ferrari C, Fabbiocchi F, De Martini S, Annoni A, Mancini ME, Formenti A, Magatelli M, Resta M, Consiglio E, Muscogiuri G, Fiorentini C, Bartorelli AL, Pepi M, Rationale and design of advantage (additional diagnostic value of CT perfusion over coronary CT angiography in stented patients with suspected in-stent restenosis or coronary artery disease progression) prospective study, *Journal of Cardiovascular Computed Tomograph* (2018), doi: 10.1016/j.jcct.2018.06.003.

Rationale and Design of ADVANTAGE (Additional Diagnostic Value of CT Perfusion over Coronary CT Angiography in Stented Patients with Suspected In-stent Restenosis or Coronary Artery Disease Progression) Prospective Study

Short Title: CTP for coronary stents

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I assure that no relationship with industry and no competing interests exist.

ABSTRACT

Background. Recent studies demonstrated a significant improvement in the diagnostic performance of coronary CT angiography (CCTA) for the evaluation of in-stent restenosis (ISR). However, coronary stent assessment is still challenging, especially because of beam-hardening artifacts due to metallic stent struts and high atherosclerotic burden of non-stented segments. Adenosine-stress myocardial perfusion assessed by CT (CTP) recently demonstrated to be a feasible and accurate tool for evaluating the functional significance of coronary stenoses in patients with suspected coronary artery disease (CAD). Yet, scarce data are available on the performance of CTP in patients with previous stent implantation.

Aim of the study. We aim to assess the diagnostic performance of CCTA alone, CTP alone and CCTA plus CTP performed with a new scanner generation using quantitative invasive coronary angiography (ICA) and invasive fractional flow reserve (FFR) as standard of reference.

Methods. We will enroll 300 consecutive patients with previous stent implantation, referred for non-emergent and clinically indicated invasive coronary angiography (ICA) due to suspected ISR or progression of CAD in native coronary segments. All patients will be subjected to stress myocardial CTP and a rest CCTA. The first 150 subjects will undergo static CTP scan, while the following 150 patients will undergo dynamic CTP scan. Measurement of invasive FFR will be performed during ICA when clinically indicated.

Results. The primary study end points will be: 1) assessment of the diagnostic performance (diagnostic rate, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy) of CCTA, CTP, combined CCTA-CTP and concordant CCTA-CTP vs. ICA as standard of reference in a territory-based and patient-based analysis; 2) assessment of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic

accuracy of CCTA, CTP, combined CCTA-CTP and concordant CCTA-CTP vs. invasive FFR as standard of reference in a territory-based analysis.

Conclusions. The ADVANTAGE study aims to provide an answer to the intriguing question whether the combined anatomical and functional assessment with CCTA plus CTP may have higher diagnostic performance as compared to CCTA alone in identifying stented patients with significant ISR or CAD progression.

KEYWORDS

CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CTP = computed tomography perfusion; ED = effective dose; FFR = fractional flow reserve.

Introduction.

Percutaneous coronary intervention (PCI) is the most common invasive cardiovascular procedure performed worldwide, as confirmed by the 528.000 and 854.000 interventions performed every year in the United States and in Europe, respectively (1). Currently, drug-eluting stents are used in more than 90% of all PCI mainly because of their positive outcomes stemming from the ability to treat complex lesions, prevent vessel recoil and abrupt occlusion and significantly decrease the risk of in-stent restenosis (ISR) and target lesion revascularization. Computed coronary tomography angiography (CCTA) is not recommended in patients with coronary stents aside from selected cases because of high rates of non-diagnostic results (2), mainly due to artifacts resulting from the metallic stent struts and fast coronary artery motion. Indeed, high and irregular heart rates enhance artifacts caused by metallic stents (3). Moreover, the recent availability of stents for treatment of small vessels (i.e. <2.50mm) (4) makes it even more difficult to reliably detecting coronary ISR by CCTA. In addition, patients treated with stenting often have increased CAD prevalence and high atherosclerotic burden of non-stented segments that further affect CCTA interpretability and accuracy. Stress myocardial computed tomography perfusion (CTP) has recently emerged as a promising strategy to combine anatomical and functional evaluation in one technique (5). Although a robust literature has demonstrated that CTP may improve CCTA diagnostic accuracy for detecting flow limiting coronary stenoses (6-11), very limited data are available on potential additional diagnostic value of CTP plus CCTA in patients previously treated with coronary stent implantation (12). Recently, a scanner that combines 0.23 mm spatial resolution, a new generation of iterative reconstruction, fast gantry rotation time and intra-cycle motion-correction algorithm for improving temporal resolution was introduced in the clinical field. The scanner has the potential to address the challenges of

coronary motion artifacts due to high HR and HR variability (13) and to combine high-spatial resolution imaging of coronary stents with myocardial perfusion assessment (14).

Aim of the present study is to assess the diagnostic performance of CCTA alone, CTP alone and CCTA plus CTP using the above-mentioned scanner with invasive coronary angiography (ICA) and invasive FFR (IFFR) as standard of reference.

2. Study design and patient population

Consecutive patients with a history of previous coronary stent implantation and referred for non-emergent and clinically indicated ICA due to suspected ISR or progression of CAD in native coronary segments will be considered for enrollment in the study. Figure 1 and Table 1 show the study design and exclusion criteria, respectively. In total, 300 patients will be subjected to a rest and stress myocardial CTP and a rest CCTA. The first 150 patients will undergo a static CTP scan, while the following 150 patients will be subjected to a dynamic CTP scan. The study protocol has received ethics committee approval and has been registered with the number R509/16-CCM 536. Written informed consent will be obtained from all patients who will be asked to refrain from smoking and caffeine for 24 hours and to maintain fasting for 6 hours before the scan. Before imaging, a rest 12-lead ECG and a revision of previous echocardiography, cardiac magnetic resonance o nuclear imaging were performed in all patients to assess the presence of signs of previous myocardial infarction. Patients with sinus rhythm and HR >65 bpm before the rest scan will receive metoprolol intravenously with a titration dose up to 15 mg to achieve a target HR <65 bpm. However, HR >65 bpm and atrial fibrillation will not be exclusion criteria. Moreover, all patients will receive sublingual nitrates to ensure coronary vasodilatation.

3.1. Rest CCTA performance and interpretation

We will perform CCTA and CTP with a 256-detector row scanner capable of whole heart coverage in one beat (Revolution CT, GE Healthcare, Milwaukee, WI). Rest CCTA will be carried out according to the recommendations of the Society of Cardiovascular Computed Tomography (15). All patients will receive a 50-ml bolus of Iodixanol 320 (Visipaque 320 mg/ml, GE Healthcare, Oslo, Norway) at an infusion rate of 6.2 ml/s followed by 50 ml of saline solution with a scan window based on HR. A BMI-adapted scanning protocol was used: BMI<20 Kg/m2, tube voltage and tube current of 100 kVp and 500mA, respectively; 20≤BMI<25 Kg/m2, tube voltage and tube current of 100 kVp and 550mA, respectively; 25≤BMI<30 Kg/m2, tube voltage and tube current of 100 kVp and 600 mA, respectively; 30≤BMI<35 Kg/m2, tube voltage and tube current of 120 kVp and 650mA, respectively, as previously described (16). Data sets of each CCTA examination will be transferred to an image-processing workstation (Advantage Workstation Version 4.7, GE Healthcare, Milwaukee, WI) and analyzed by two readers, both with over 10 years of clinical experience in CCTA performance and analysis, blinded to the clinical findings. For any disagreement in data analysis between the two readers, consensus agreement will be achieved. According to SCCT guidelines for reporting (15), image quality, plaque characteristics, severity of coronary lesions and ISR will be evaluated. A stenosis and/or an ISR >50% will be considered significant when assessing anatomy in the rest CCTA. Moreover, an additional cut-off of >70% stenosis will be used to assess the lesions in native vessels. Finally, high risk plaque features (HPFs) were evaluated as follow: arterial remodeling

index (RI) assessed using vessel area (RIa = lesion plaque area/reference area), plaque burden (PB = [lesion plaque area-lesion lumen area]/lesion plaque area), napkin ring sign (NRS) defined as the presence of a semicircular thin enhancement around the plaque along the outer contour of the vessel and small spotty calcifications (SC) as any discrete calcification ≤3 mm in length and occupying ≤90° arc when viewed in short axis. Plaque length was recorded as well. Plaque consistency was assessed using Hounsfield Unit (HU) and low-attenuation plaque (LAP) was defined as the presence of any voxel <30 HU. Total plaque volume was evaluated and reported in mm3. Low attenuation plaque volume and non-calcified fibro-fatty plaque volume have been expressed as the amount of plaque with <30 HU and <150 HU, respectively, reported in mm3, as previously described (17).

3.2 Stress myocardial static CTP performance and interpretation

Figure 2 shows the stress myocardial CTP acquisition protocol. Vasodilatation will be induced with i.v. adenosine injection (0.14 mg/Kg/min over 4 min). Using the same technique described for rest CCTA, a single stress CTP scan will be acquired during first-pass enhancement. The myocardium will be evaluated on short-axis (apical, medium and basal slices) and long-axis views (2-, 3- and 4-chamber projections) with 8-mm thick average multi-planar reformatted images. A narrow window width and level (350 W and 150 L) will be used for perfusion defect evaluation. Each myocardial segment will be correlated to the specific coronary territory as described by Cerci et al. (18). True perfusion defects will be qualitatively defined as subendocardial hypoenhancement encompassing >25% of transmural myocardial thickness within a specific coronary territory. Patients will be considered to test positive for myocardial

ischemia in the event stress myocardial static CTP shows worsening as compared with rest CTP in more than one myocardial segment (6).

3.3 Stress myocardial dynamic CTP performance and interpretation

Vasodilatation will be induced with the same protocol described for stress myocardial static CTP. At the end of the third minute of adenosine infusion, multiple sequential scans of myocardial attenuation (one scan every three seconds for a total breath hold of 30 seconds) will be acquired with the same scan parameters as described for rest CCTA. Evaluation of the myocardium will be performed as described for stress myocardial static CTP. In addition, the myocardial blood flow (MBF) will be calculated by using the deconvolution maps technique, as the results of the following measurements: MBF = Blood volume (Intravascular + Extravascular volume) / the Mean transit time (the time between arterial inlet and venous outlet) (11). A value below 75 ml/100 ml/min will be used to identify hemodynamically significant ISR and/or coronary artery stenosis (11).

3.4. ICA and invasive FFR performance and interpretation.

In all patients, diagnostic ICA will be performed within 60 days after CCTA examination by certified interventional cardiologists following usual clinical indications and imaging standards set forth by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Society for Cardiac Angiography and Interventions (19). Quantitative coronary angiography (QCA) (QantCor QCA; Pie Medical Imaging, Maastricht, the Netherlands) analysis will be performed at the vessel level. Images will be analyzed by two interventional cardiologists, both with over 10 years of clinical experience in QCA performance

and analysis, blinded to the CCTA-CTP findings. For any disagreement in data analysis between the two readers, consensus agreement was achieved. Measurement of invasive FFR will be performed during ICA when clinically indicated, at the discretion of the interventional cardiologist according to standard practice (20). Invasive FFR<0.8 will be the threshold used to define ischemia in the interrogated artery and its supplied territory.

3.5. Radiation exposure.

For CCTA, the effective radiation dose (ED) will be calculated by multiplying the dose-length product by a conversion coefficient for the chest (K = 0.014 mSv/mGy cm). For ICA, the ED will be calculated by multiplying the dose-area product by a conversion factor (K = 0.21 mSv/mGy cm2) for lateral and postero-anterior radiation exposure in the chest area. The expected ED for static and dynamic myocardial CTP including rest and stress datasets should range between 2 and 6 mSv and 6 and 10 mSv, respectively.

3.6 CCTA and CTP analyses

For each cardiac CT, the following parameters will be evaluated:

a) **Diagnostic rate.** The diagnostic rate of CCTA, CTP and the combined evaluation CCTA-CTP in stent-based, territory-based and patient-based analyses will be assessed.
   - The diagnostic rate of CCTA in a stent-based analysis will be defined as the number of stents interpretable/number of stents evaluated. The diagnostic rate of CCTA in a territory-based analysis will be defined as the number of coronary territories interpretable/number of territories evaluated. Each coronary territory will be considered interpretable if any coronary segments included in that territory will be interpretable. The diagnostic rate of CCTA in a patient-based analysis will be defined

as the number of patients interpretable/number of patients evaluated. Each patient will be considered interpretable if all coronary tree including stented and non-stented segments will be free from severe artifacts and then judged as interpretable.

- The diagnostic rate of CTP in a stent-based analysis will be defined as the number of stents interpretable in terms of myocardial perfusion assessment/number of stents evaluated. The diagnostic rate of CTP in a territory-based analysis will be defined as the number of coronary territories interpretable in terms of perfusion assessment/number of territories evaluated. The diagnostic rate of CTP in a patient-based analysis will be defined as the number of patients interpretable/number of patients evaluated. Each patient will be considered interpretable if all coronary territories will be interpretable in terms of perfusion assessment.
- The diagnostic rate of the combined assessment CCTA-CTP in a stent-based analysis will be defined as the number of stents interpretable in terms of anatomy and/or positioned in a coronary territory interpretable in terms of perfusion/number of stents evaluated. The diagnostic rate of CCTA-CTP in a territory-based analysis will be defined as the number of coronary territories in which any coronary segments included in that territory will be interpretable in terms of anatomy and/or interpretable in terms of perfusion/number of territories evaluated. The diagnostic rate of CCTA-CTP in a patient-based analysis will be defined as the number of patients interpretable/number of patients evaluated. Each patient will be considered interpretable if all coronary segments will be judged assessable in terms of anatomy and/or all coronary territories will be estimated interpretable in terms of perfusion assessment.

b) Diagnostic Accuracy.

b 1) Diagnostic accuracy vs. QCA by using stents, territories and patients interpretable only for the analysis.

- We will assess sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CCTA, CTP, combined evaluation CCTA-CTP and concordant evaluation CCTA-CTP vs. QCA as standard of reference in a stent-based, territory-based and patient-based analysis.
- Regarding the evaluation of CCTA diagnostic accuracy vs. QCA, CCTA will be considered positive in the presence of a >50% ISR in a stent-based analysis, of >50% stenosis in native segment and/or >50% ISR in the same coronary territory in a territory-based analysis, and of >50% stenosis and/or >50% ISR in any coronary native segment/stent in a patient-based analysis.
- Regarding the CTP diagnostic accuracy vs. QCA, CT examination will be considered positive in the presence of a perfusion defect in a territory including a stent segment in a stent-based analysis, in a specific coronary territory in a territory-based analysis and in any type of coronary territory in a patient-based analysis.
- Regarding the diagnostic accuracy of combined CCTA-CTP vs. QCA, CCTA-CTP will be considered positive in the presence of a >50% ISR and/or a perfusion defect in the territory including that specific stent segment in a stent-based analysis, a >50% stenosis in native segment and/or a >50% ISR in a specific coronary territory and/or a perfusion defect in the same coronary territory in a territory-based analysis and a >50% stenosis in native segment and/or a >50% ISR in any coronary vessel and/or a perfusion defect in any type of coronary territory in a patient-based analysis.

- Regarding the diagnostic accuracy of concordant CCTA-CTP vs. QCA, concordant CCTA-CTP will be considered positive in the presence of a >50% ISR and a perfusion defect in the territory including that stent segment in a stent-based analysis, a >50% stenosis in native segment and/or a >50% ISR in a specific coronary territory and a perfusion defect in the same coronary territory in a territory-based analysis and a >50% stenosis in native segment and/or a >50% ISR in any coronary vessel and a perfusion defect in any type of coronary territory in a patient-based analysis. Figure 3 shows an example of a concordant assessment of a significant stenosis in the left anterior descending coronary artery.

- **b 2) Diagnostic accuracy vs. QCA by using all stents, territories and patients for the analysis, with non-interpretable stents, territories and patients censored as positive.**
- We will assess sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CCTA, CTP, combined evaluation CCTA-CTP and concordant evaluation CCTA-CTP vs. QCA as standard of references in a stent-based, territory-based and patient-based analysis.

- **b 3) Diagnostic accuracy vs. invasive FFR.**

  We will assess sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CCTA, CTP, combined evaluation CCTA-CTP and concordant evaluation CCTA-CTP vs. IFFR as standard of reference in a vessel-based analysis.

3.7 Study End points

Primary end points:

a) Assessment of the diagnostic performance (diagnostic rate, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy) of CCTA, CTP, combined CCTA-CTP and concordant CCTA-CTP vs. QCA as standard of reference in a territory-based and patient-based analysis (by using both interpretable data for the analysis only and all data for the analysis).

b) Assessment of the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CCTA, CTP, combined CCTA-CTP and concordant CCTA-CTP vs. IFFR as standard of reference in a vessel-based analysis.

Secondary end points:

a) Assessment of the diagnostic performance (diagnostic rate, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy) of CCTA, CTP, combined CCTA-CTP and concordant CCTA-CTP vs. QCA as standard of reference in a stent-based analysis (by using both interpretable data for the analysis only and all data for the analysis).

3.8 Statistical analysis

The whole population of the study will be of 300 patients, taking into consideration two different cohorts of static and dynamic CTP that are scheduled to be enrolled in a sequential fashion. Accordingly, the sample size has been calculated for each single cohort separately. Assuming a 40% prevalence of significant ISR or “de novo” stenoses in native coronary

segments and a diagnostic accuracy of 80% for CTP vs. QCA in a territory-based model, a sample size of 150 patients is estimated as necessary to identify a difference of 8% between stress myocardial CTP and CCTA for detecting significant ISR or CAD progression at QCA at a significance level of 5% and at least 80% power. For all patients, per-stent, per-territory and per-patient sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CCTA, CTP and combined and concordant CCTA/CTP will be calculated with 95% confidence intervals and compared with the McNemar's test for dependent proportions. In the territory-level analysis, the data from different segments are pooled and the sensitivity, specificity, positive predictive value, negative predictive value and accuracy estimates adjusted for correlation within patients will be modeled using the generalized estimating equation approach. A P-value of less than 0.05 will be considered statistically significant. Statistical analysis will be performed with SPSS, version 24 (SPSS Inc, Chicago, IL) and R version 3.3.0.

Current status of the study

The study received the ethics committee approval (number R509/16-CCM 536) in December 2016. The patient enrollment started in January 2017 and nowadays 140 out of 150 expected patients in the static cohort have been enrolled.

Discussion

Although CCTA has emerged as a reliable tool for CAD diagnosis, visualization of coronary stent lumen and quantification of ISR with CCTA has been hindered by beam-hardening artifacts, caused by metallic stent struts and vessel calcification, leading to a 9-10% rate of non-assessable stents reported by previous meta-analyses (21,22). The introduction in the clinical field of scanners equipped with increased spatial resolution along the X-Y planes and iterative reconstruction algorithm allowed for improved visualization of stent lumen and better stent

interpretability, without significant improvement in diagnostic accuracy (23). Moreover, the high atherosclerotic burden, frequently associated with vessel wall calcification, commonly affecting non-stented segments of patients with previous PCI, is another cause of low assessability and diagnostic power of CCTA in this clinical setting, as it happens for patients with a high pretest likelihood of CAD (24). For these reasons, functional appraisal in addition to anatomical evaluation could be of great help for properly assessing patients who underwent complex and sometimes repeated PCI with stent implantation. The combined approach may improve CCTA diagnostic accuracy but also enhance patient management and prognostic stratification, leading to a correct indication of whether to subject the patient to further intervention. Recently, stress myocardial CT perfusion (CTP) and fractional flow reserve CT-derived (FFR_{CT}) have been introduced in the clinical field as new tools for evaluating the functional relevance of coronary stenoses with cardiac CT. FFR_{CT} does not require additional scan or use of stressors and, therefore, is associated with low radiation exposure. However, it is based on geometric and physiological assumptions and, more importantly, it has not yet demonstrated to be able of assessing patients with coronary stents (25). Stress myocardial CTP is potentially more suitable for evaluating the ischemic cascade physiology and may provide information on both macrovascular and microvascular disease status, but requires an additional scan, use of a stressor agent, and is associated with higher radiation exposure (26). The ADVANTAGE study aims to provide an answer to the intriguing question whether the combined anatomical and functional assessment with CCTA plus CTP may have higher diagnostic performance (diagnostic rate and diagnostic accuracy) as compared to CCTA alone in identifying stented patients with significant ISR or “de novo” stenoses. Moreover, the study is designed to provide useful information about the diagnostic accuracy of CTP and of the combined CCTA-CTP for detecting flow limiting “de

novo" lesions. One interesting feature of the study is the use of a new scanner generation that, combining a 0.23 mm spatial resolution, a new generation of iterative reconstruction, fast gantry rotation time, an intra-cycle motion-correction algorithm and a 16-cm Z-axis coverage, allows to scanning all heart in one single cardiac beat, irrespectively from HR and heart rhythm. This is of particular benefit for CTP assessment in terms of both radiation exposure and diagnostic accuracy (14, 27-30). Indeed, radiation exposure resulting from stress CTP performed with this scanner in a static modality is very low (<5 mSv for the whole cardiac-CT assessment), if one considers the ED values reported for CCTA in recent studies performed in patients with high HR and/or AF during scanning. In these studies, ED values ranged between 3 and 4 mSv, in relationship with the wide acquisition window applied (500 msec) that is the same we will use for stress CTP (28-30). If the ADVANTAGE study will confirm expectations in terms of radiation exposure and high diagnostic performance in a patient-based model, the combined CCTA-CTP diagnostic approach may become a new clinical tool for patient follow-up after previous implantation of coronary stents.

Study limitations.

Some limitations of this study should be acknowledged. First, the ADVANTAGE is a prospective study on the assessment of CCTA-CTP in patients with previous stent implantation who are referred for a clinically indicated ICA because of suspected ISR or progression of CAD in native vessels. For this reason, the diagnostic performance of CCTA-CTP provided by the study results could be different from that obtainable in other clinical settings, e.g. in patients without symptoms or signs of myocardial ischemia. Second, because the invasive FFR will be performed when clinically indicated only, we will not able to compare the CTP findings with the

invasive gold standard in terms of functional assessment of the stenosis in the whole study population. However, we will perform a subanalysis comparing the diagnostic accuracy of perfusion defects detected by CTP to the results of other non-invasive stress tests in the subgroup of patients in whom the clinical indication to ICA will be made based on pathological findings at non-invasive stress imaging tests (stress echocardiography, stress cardiac magnetic resonance, nuclear imaging). Third, we recognize that a double-blind randomized enrollment 1:1 static vs. dynamic cohorts would be the better fashion to compare the usefulness of static vs. dynamic approach of CTP. However, when the study started in our Institute, the final version of the dedicated software for the post-processing of dynamic CTP was not available. In order to avoid risk of blinding and learning bias due to the sequential enrollment, different readers between static and dynamic cohorts will be dedicated to assess CTP images.

Funding.

The study has received a grant from General Electric (GE Healthcare, Milwaukee, WI) registration number of the study is R509/16-CCM 536. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Conflicts of interest.

Daniele Andreini declares the following conflict of interest: speaker bureau for GE Healthcare.

Gianluca Pontone declares the following conflict of interest: speaker bureau for GE Healthcare, Bracco, Medtronic; consultant for GE Healthcare. Carlos Collet reports receiving research grants from Heart Flow Inc and Biosensor.

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Table 1

Exclusion criteria
Prior clinically documented myocardial infarction
Suspicion of acute coronary syndrome;
Need of an emergent procedure within 48 hours of presentation
Evidence of clinical instability
Contra-indications for contrast agents or impaired renal function
Inability to sustain a breath hold
Pregnancy
Body mass index > 35 kg/m2
Presence of a pacemaker or implantable cardioverter defibrillator
Contra-indications to the administration of sub-lingual nitrates, b-blockade and adenosine

Figure Legends

Figure 1. ADVANTAGE study workflow.

CTP: computed tomography perfusion; FFR: fractional flow reserve; ICA: invasive coronary angiography.

Figure 2. Stress myocardial CTP plus rest CCTA protocol.

See “Stress myocardial static CTP performance and interpretation” and “Rest CCTA performance and interpretation” paragraphs for further detail.

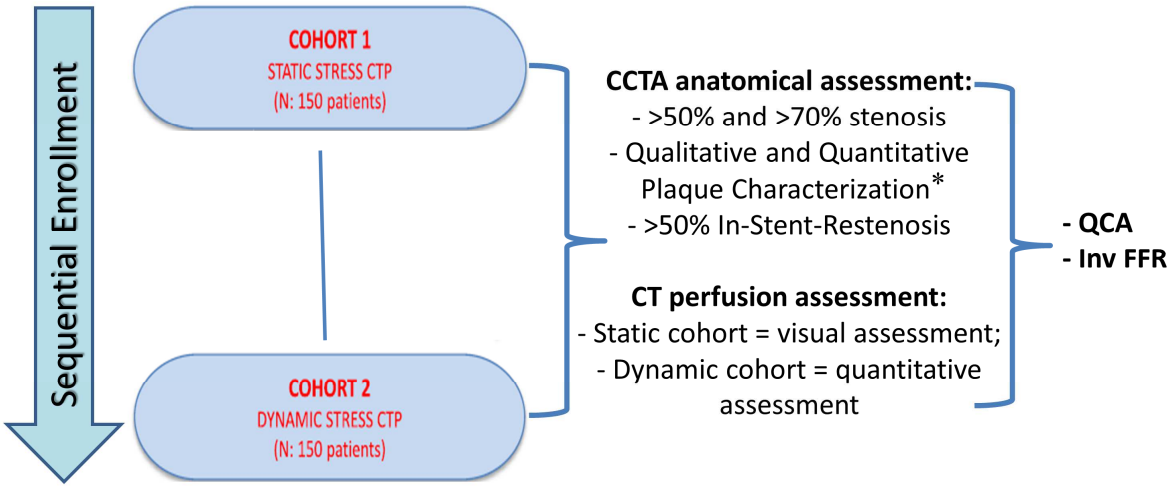
CCTA: cardiac computed tomography angiography; CTP: computed tomography perfusion.

Figure 3. Concordant CCTA-CTP.

Panel A: CCTA assessment of LCx, showing absence of “de novo” stenosis and/or ISR of the stent implanted in the distal part of the vessel. Panel B: CCTA assessment of LAD, showing a >50% stenosis in the mid portion of the vessel, confirmed by the cross sections in correspondance of the lesion and at the distal reference segment, respectively (Panel C and D, respectively). Panel E and F: CTP assessment, showing a concordant transmural perfusion defect of the anterior septum, depicted in long axis and short axis views, respectively.

LAD: left anterior descending artery; LCx: Left circumflex artery.

Consecutive patients with previous stent implantation scheduled for a non-emergent clinically indicated invasive coronary angiography for suspected in-stent restenosis or de novo stenosis in native coronary arteries



*-High-risk plaque features (positive remodelling, plaque burden, spotty calcification, napkin ring sign)

- Total plaque volume (mm^3), low attenuation plaque volume (<30 HU), non-calcified plaque volume (<150 HU)