



Research paper

Rationale and design of the worldwide prospective multicenter registry on radiation dose estimates of cardiac CT angiography in daily practice in 2017 (PROTECTION VI)



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ABSTRACT

Background: Cardiac computed tomography angiography (cardiac CTA) is an increasingly used versatile imaging method to evaluate coronary and cardiac morphology. Owing to improvements in technology, image quality has continuously improved over the last 10–20 years. At the same time, numerous non-randomized and randomized studies have been performed to reduce the associated radiation exposure. Currently, it is unclear if the advances in technology and knowledge about radiation reduction translated into reduced levels of cardiac CTA radiation dose in daily clinical practice as well as a wide utilization of dose-saving strategies.

Methods: The PROTECTION VI study is a multicenter, prospective, worldwide registry designed to evaluate radiation dose exposure, utilization of dose-saving strategies and diagnostic image quality during cardiac CTA in current daily practice. Assessment of image quality will be addressed by the evaluation of diagnostic image quality at the local study site and the calculation of quantitative image quality parameters in an imaging core laboratory. Above 4000 patients will be enrolled from approximately 70 sites in Europe, North America, South America, Asia and Australia. The study will analyze median radiation dose levels, image quality, frequency of use and efficacy of algorithms for dose reduction, and patient and study-related predictors associated with radiation dose.

Conclusions: The PROTECTION VI study is designed to provide a reliable estimate of current radiation dose for cardiac CTA and to assess the potential for additional dose reductions.

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1. Introduction

Cardiac computed tomography angiography (cardiac CTA) has emerged as a noninvasive imaging method with numerous indications and fields of application.^{1,2} Most commonly, cardiac CTA is used for the evaluation of the coronary arteries to diagnose coronary artery stenosis. In particular, for patients with suspected coronary artery diseases, coronary CTA reaches high sensitivity and negative predictive value, thereby possibly avoiding invasive coronary angiography.³ Due to the rapidly increasing volume of cardiac CTAs performed, safety considerations are an important concern, especially for the cohort of younger patients with low likelihood of disease. In this regard, ionizing radiation exposure during cardiac CTA has to be taken into account, because this is known to potentially amplify long-term carcinogenesis in a dose-dependent manner.⁴ One decade ago, the radiation dose exposure of cardiac CTA in daily clinical practice was evaluated in a large prospective multicenter registry (PROTECTION I study).⁵ Shortly before that time, 64-slice CT scanners had been introduced and dual-source CT scanning became available, enabling improved imaging of cardiac morphology and function at higher temporal resolution.^{6,7} In 2007, radiation doses during cardiac CTA varied substantially between study sites, and the utilization of dose-saving protocols differed significantly.⁵ This suggested a large potential for dose reduction in cardiac CTAs.

Since 2007, dose-saving strategies and protocols have been widely implemented, paving the way for potential reductions of radiation dose exposure (Table 1a). Improved CT modifications and software include low tube current imaging, decreased tube voltage, automatic dose modulation with tube current adjustment to the patients' size and shape and electrocardiography (ECG)-controlled tube current modulation.^{8,9} Another major improvement has been the utilization of iterative image reconstruction with advanced raw data processing, which leads to decreased image noise in low-contrast areas and enables additional radiation dose reduction.¹⁰ Improved cardiac CTA protocols with radiation exposure only during mid-diastole (prospectively ECG-triggered axial scanning) or solely during one cardiac cycle (prospectively ECG-triggered high-pitch spiral scanning) further enable significant dose savings.^{11,12} Beyond that, CT hardware and design, including wide detector imaging, as well as patient- and case-related factors contribute to the level of radiation dose exposure (Table 1b). Certainly, utilization of ionizing radiation always has to be considered critically and the use of appropriateness and acquisition guidelines is recommended in clinical decision-making.^{13,14}

Cardiologists and radiologists utilize the procedural improvements described to minimize radiation dose, whilst still maintaining diagnostic image quality. Thus, clinicians aim to reduce radiation dose

exposure to be “as low as reasonably achievable” (ALARA principle).¹⁵ Since 2007, several randomized clinical trials have demonstrated the maintenance of diagnostic image quality for the utilization of different dose-saving techniques in cardiac CTA imaging.^{12,16–20} These studies also proved that dose-saving techniques may be combined using CT platforms from different vendors. Recent experimental single-center data demonstrated a tremendous reduction of radiation dose exposure in cardiac CTA in carefully selected patients.^{21,22} Since 2007, however, no studies have investigated the radiation dose exposure associated with cardiac CTA in daily practice in a large, multicenter approach and acquired data for comprehensive evaluation of various dose-saving techniques and their impact on image quality. We therefore designed an international prospective multicenter study, PROTECTION VI, to evaluate radiation dose exposure and the application of dose-saving strategies worldwide. We herein report the objectives, methodology, and rationale for this study.

2. Overall study design

The PROTECTION VI trial is a prospective, worldwide, multicenter, observational, and multi-vendor registry evaluating the radiation dose exposed from cardiac CTA in current daily practice. The study is independent from industry funding.

3. Participating study sites

For this study cardiologists and radiologists from all around the world have been invited to participate. The invited colleagues have been identified by literature research to the topic of cardiac CT imaging with publication date between January 2015 and December 2016 as well as prior participation at PROTECTION I. Additionally, we invited active members of the Society of Cardiovascular Computed Tomography (SCCT) who published articles in the field of cardiac imaging and radiation dose. With the objective to achieve a representative and balanced study cohort from as many different countries and backgrounds as possible, we invited 435 colleagues from 62 different countries by email to participate in PROTECTION VI. Although no supportive funding has been offered, a total of 70 clinical institutions from 34 different countries are expected to participate in this study. The four main CT scanner manufactures Siemens Healthcare (Erlangen, Germany), GE Healthcare (Buckinghamshire, United Kingdom), Toshiba Medical Systems Corporation (Ōtawara, Japan) and Philips Healthcare (Amsterdam, The Netherlands) are represented in the participating study sites. Each study site consulted the responsible local ethics committee to evaluate the study protocol, which had to be approved prior to patient enrollment. For US and Canadian sites, the possibility of a centralized institutional review board (IRB) process has been installed by the National Institutions of Health (NIH) in Bethesda, Maryland. The number of enrolled patients per site is expected to vary, but no institution will enroll more than 10% of the total number of subjects.

4. Target population

The study is targeted to subjects undergoing cardiac CT angiography in daily clinical routine. Inclusion criteria are a clinical indication for cardiac CTA including evaluation of the coronary arteries or other cardiac structures with scanning of the heart. Performance of cardiac CTA will be standard of clinical care without external influence by the core laboratory.

5. Study objectives

The primary objective of the PROTECTION VI study is to collect and analyze radiation dose exposure data from cardiac CTA in current daily practice. It will also assess the variability of radiation dose estimates

Table 1
(a) Dose-saving strategies in CCTA imaging. (b) Pre-requisites for the application of dose-saving strategies and contributing factors to the level of radiation dose exposed.

a) Dose-saving strategies in CCTA imaging	b) Requirements and contributing factors to radiation dose exposure
CT adjustment and software:	CT hardware and design:
<ul style="list-style-type: none"> ● Low tube current imaging ● Low tube potential imaging ● Automatic dose modulation ● ECG-controlled tube current modulation ● Iterative image reconstruction 	<ul style="list-style-type: none"> ● Powerful X-ray generators ● Dual-source CT scanning with spectral pre-filtration ● Advanced X-ray detectors with anti-scatter grids
CT protocols:	Patient- and case-related factors:
<ul style="list-style-type: none"> ● Prospective ECG-triggered axial (sequential) scanning ● Prospective ECG-triggered high-pitch spiral scanning 	<ul style="list-style-type: none"> ● Patient body mass index (BMI) ● Optimal patient positioning (ideally at CT gantry isocenter) ● Use of appropriateness guidelines

Table 2
Primary and secondary study endpoints.

Primary endpoint
1. Radiation dose estimates of cardiac CT angiographies (CCTA) in daily practice
Secondary endpoints
1. Variation of radiation dose estimates between
1.1. a. Participating study sites, 1.1.b. countries and 1.1.c. continents
1.2. CT systems
1.3. CT vendors
2. Experience of study sites in relation to radiation dose
3. CCTA scan length and relationship between scan and heart length
4. Application and efficacy of dose-saving strategies
5. Image quality in relation to radiation dose estimates
6. Frequency of diagnostic or non-diagnostic (repetitive) scans

between study sites, countries, continents, different CT systems and CT vendors. We will relate the experience of participating study sites to the radiation dose exposure. The cardiac CT scan length and the relationship between scan and heart length will be assessed. Specifically, the study will assess the utility of the various dose-saving strategies. Further, the relationship between image quality and radiation dose estimates will be explored. The study will also assess whether a cardiac CTA scans is diagnostic or if repeat scans are necessary. The primary and secondary endpoints of the study are summarized in Table 2.

6. Methods

6.1. Patient recruitment and evaluation

Participating study sites were asked to enroll consecutive patients and collect data that are transferred and evaluated at a central core laboratory (Fig. 1). Study sites will have enrolled all consecutive patients according to the inclusion criteria examined by cardiac CTA within one month between March and October 2017. Prior to data collection, local site investigators are obliged to request written informed consent if required by the local ethics committee or the local IRB. Data collection consists of the completion of a standardized case

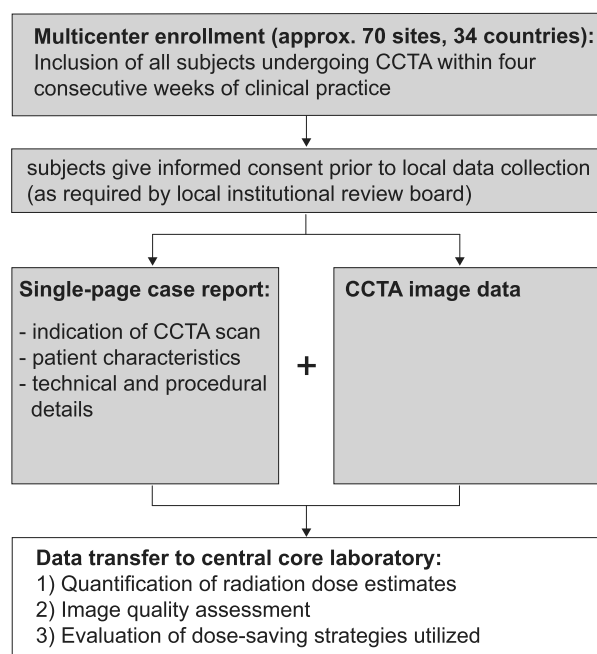


Fig. 1. Overview of the data acquisition and processing scheme including multicenter patient enrollment, data collection at local study sites, data transfer and data evaluation in a central core laboratory.

report form, cardiac CTA images and the CT protocol. The case report form may be completed by cardiologists, radiologists or trained CT technicians and includes the clinical indication of the cardiac CTA, the patient characteristics, the cardiovascular risk profile and key technical and procedural scan details such as radiation dose parameters. After completion of the cardiac CTA scan, subject participation for PROTECTION VI is finalized. No clinical follow-up is performed. Subsequently, the case report form and all cardiac CTA image data, which are used for reporting, will be transferred to the central core laboratory, where data evaluation including quantification of radiation dose estimates, image quality assessment and evaluation of dose-saving strategies will be carried out.

6.2. Estimation of radiation dose

Local investigators from the participating study sites obtain radiation dose parameters including the volume CT dose index ($CTDI_{vol}$) and the dose length product (DLP) from the scan protocol generated by the CT system after each cardiac CTA study. The effective dose will be estimated from the DLP in combination with an appropriate organ-weighting factor of the chest as the investigated anatomic region. Besides the pure estimation of the radiation dose exposed from cardiac CTA studies, influencing factors such as patient characteristics, clinical indication, scans from different CT systems and vendors, CT protocols, application of dose-saving strategies and experience of the investigators will be evaluated. Radiation dose will be calculated separately according to the clinical indication.

6.3. Measurement of image quality

Assessment of image quality includes the diagnostic evaluation of the four main coronary arteries (left main, left anterior descending, left circumflex, and right coronary artery) assessed by the local site investigator. A quantitative image quality assessment will be added after image analysis in the core laboratory. For analysis of quantitative image quality, the data set will be formatted using 1.0 mm slice thickness. The assessed parameters include signal intensity, image noise, contrast-to-noise ratio and signal-to-noise ratio. Signal intensity will be derived from the mean CT attenuation value of a circular region within the left ventricle. Image noise is defined as the averaged standard deviation of the CT attenuation value of this circular region within the left ventricle. Contrast-to-noise ratio is defined as the difference between the mean CT attenuation values within the left ventricle and the mean density of the left lateral ventricular wall, which will be divided by image noise. Signal-to-noise ratio will be calculated as mean CT attenuation value within the left ventricle divided by image noise.

6.4. Statistical considerations

Univariate and multivariate analyses will be performed to identify predictors significantly associated with radiation dose. To avoid overfitting, only variables with $p < 0.1$ in the univariate model will be entered into the multivariate model. A generalized estimation equation model will be used to account for the clustering effect of this multicenter trial. All statistical analysis will be performed using R version 3.4.1 or newer.²³

7. Organization and data management

The study protocol has been approved by each participating center and was handed to the local ethics committee or local IRB for review and approval. An Executive Steering Committee composed of a group of physicians with expertise in cardiac CTA, clinical research and statistics supervises the study. The Executive Steering Committee is tasked with oversight of the study design, conduct of the registry, final review of data as well as presentation and publication of results. This study has

been registered with clinicaltrials.gov (NCT02996903).

8. Summary and conclusions

The PROTECTION VI study will investigate the current radiation dose of cardiac CTA based on real-world clinical use. Compared to the primary estimation of radiation dose evaluated in the PROTECTION I study one decade ago, the current dose exposure during cardiac CTA is potentially lower. Yet, current real world data on radiation exposure from cardiac CTA globally is lacking as is the extent to which dose reduction strategies are being routinely employed. PROTECTION VI has been designed to assess the combination of radiation dose exposure, utility of dose-saving strategies and maintenance of diagnostic image quality. Ultimately, this study aims to evaluate the potential scope for future radiation dose reductions. In this way, the results of PROTECTION VI may contribute to achieving the lowest possible radiation dose of cardiac CTA to reduce the risk for malignancy induction whilst maintaining diagnostic image quality in an increasing population examined with cardiac CTA worldwide.

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Conflicts of interest

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