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Pilot study of the multicentre DISCHARGE Trial: image quality and protocol adherence results of computed tomography and invasive coronary angiography

Rubeis, G. de; Napp, A.E.; Schlattmann, P.; Geleijns, J.; Laule, M.; Dreger, H.; ... ;
DISCHARGE Trial Grp

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Pilot study of the multicentre DISCHARGE Trial: image quality and protocol adherence results of computed tomography and invasive coronary angiography

Gianluca De Rubeis¹ · Adriane E. Napp² · Peter Schlattmann³ · Jacob Geleijns⁴ · Michael Laule⁵ · Henryk Dreger⁵ · Klaus Kofoed^{6,7} · Mathias Sørgaard⁷ · Thomas Engstrøm⁷ · Hans Henrik Tilsted⁷ · Alberto Boi⁸ · Michele Porcu⁹ · Stefano Cossa¹⁰ · José F. Rodríguez-Palomares¹¹ · Filipa Xavier Valente¹¹ · Albert Roque¹² · Gudrun Feuchtner¹³ · Fabian Plank¹⁴ · Cyril Štěchovský¹⁵ · Theodor Adla¹⁶ · Stephen Schroeder¹⁷ · Thomas Zelesny¹⁸ · Matthias Gutberlet¹⁹ · Michael Woinke²⁰ · Mihály Károlyi²¹ · Júlia Karády²² · Patrick Donnelly²² · Peter Ball²³ · Jonathan Dodd²⁴ · Mark Hensey²⁵ · Massimo Mancone²⁶ · Andrea Ceccacci²⁶ · Marina Berzina²⁷ · Ligita Zvaigzne²⁸ · Gintare Sakalyte²⁹ · Algidas Basevičius³⁰ · Małgorzata Ilnicka-Suckiel³¹ · Donata Kuśmierz³² · Rita Faria³³ · Vasco Gama-Ribeiro³³ · Imre Benedek³⁴ · Teodora Benedek³⁴ · Filip Adjić³⁵ · Milenko Čanković³⁶ · Colin Berry³⁷ · Christian Delles³⁷ · Erica Thwaite³⁸ · Gershan Davis³⁹ · Juhani Knuuti⁴⁰ · Mikko Pietilä⁴¹ · Cezary Kepka⁴² · Mariusz Kruk⁴³ · Radosav Vidakovic⁴⁴ · Aleksandar N. Neskovic⁴⁴ · Iñigo Lecumberri⁴⁵ · Ignacio Diez Gonzales⁴⁶ · Balazs Ruzsics⁴⁷ · Mike Fisher⁴⁷ · Marc Dewey² · Marco Francone^{1,48} · The DISCHARGE Trial Group

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Abstract

Objective To implement detailed EU cardiac computed tomography angiography (CCTA) quality criteria in the multicentre DISCHARGE trial (FP72007-2013, EC-GA 603266), we reviewed image quality and adherence to CCTA protocol and to the recommendations of invasive coronary angiography (ICA) in a pilot study.

Materials and methods From every clinical centre, imaging datasets of three patients per arm were assessed for adherence to the inclusion/exclusion criteria of the pilot study, predefined standards for the CCTA protocol and ICA recommendations, image quality and non-diagnostic (NDX) rate. These parameters were compared via multinomial regression and ANOVA. If a site did not reach the minimum quality level, additional datasets had to be sent before entering into the final accepted database (FADB).

Results We analysed 226 cases (150 CCTA/76 ICA). The inclusion/exclusion criteria were not met by 6 of the 226 (2.7%) datasets. The predefined standard was not met by 13 of 76 ICA datasets (17.1%). This percentage decreased between the initial CCTA database and the FADB (multinomial regression, 53 of 70 vs 17 of 75 [76%] vs [23%]). The signal-to-noise ratio and contrast-to-noise ratio of the FADB did not improve significantly (ANOVA, $p = 0.20$; $p = 0.09$). The CTA NDX rate was reduced, but not significantly (initial CCTA database 15 of 70 [21.4%]) and FADB 9 of 75 [12%]; $p = 0.13$).

Conclusion We were able to increase conformity to the inclusion/exclusion criteria and CCTA protocol, improve image quality and decrease the CCTA NDX rate by implementing EU CCTA quality criteria and ICA recommendations.

Key Points

- Failure to meet protocol adherence in cardiac CTA was high in the pilot study (77.6%).
- Image quality varies between sites and can be improved by feedback given by the core lab.
- Conformance with new EU cardiac CT quality criteria might render cardiac CTA findings more consistent and comparable.

Keywords Medical imaging · CT angiography · Angiography, coronary · Coronary artery disease · Trial protocols

✉ Marco Francone
marco.francone@uniroma1.it

Extended author information available on the last page of the article

Abbreviations

BMI	Body mass index
CABG	Coronary artery bypass grafting
CACS	Coronary artery calcium score
CAD	Coronary artery disease

CCTA	Cardiac CT angiography
CNR	Contrast-to-noise ratio
DLP	Dose-length product
FBP	Filtered back projection
FOV	Field of view
HR	Heart rate
HU	Hounsfield units
ICA	Invasive coronary angiography
IR	Iterative reconstruction
LV	Left ventricle
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomised controlled trial
ROI	Region of interest
RV	Right ventricle
SD	Standard deviation
SNR	Signal-to-noise ratio

Introduction

The DISCHARGE (Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies) trial is a collaborative multinational research project funded by the 7th Framework Programme of the European Union (FP7/2007-2013, grant agreement EC-GA 603266). Its main aim is to guide clinicians in choosing between invasive coronary angiography (ICA) and cardiac computed tomography angiography (CCTA) [1, 2] for the diagnostic evaluation of patients with stable chest pain and an intermediate risk of cardiovascular disease. The current diagnostic gold standard in this subset of patients is ICA [3–6]. However, obstructive coronary artery disease is detected in only about 42% of elective cardiac catheterisations [7]. To investigate a safer alternative for these redundant and invasive examinations (1.27% rate of adverse events [8]), the DISCHARGE trial was set up. The consortium includes 25 clinical centres with a recognised experience in cardiac imaging from 16 European countries using different scanners' generations from different manufacturers.

According to the principles of justification of practice and optimization of protection, earlier investigators analysed the interdependent relationship between radiation dose and image quality in cardiac CTA, being concerned about the significant radiation burden associated with previous CT generations [9–13]. Image quality was therefore reported as an indicator of radiation dose reduction efficacy and often analysed using qualitative scales [14–17].

In contrast to these earlier approaches, we believe that image quality has a pivotal role in developing a standardised cardiac CTA protocol, particularly when a multicentre and multivendor protocol is meant to be set up. Protocol adherence and standardization of image quality are mandatory in large

trials to allow inter- and intra-patient comparison of patients included in a clinical trial.

Diagnostic quality and patient's safety are, in fact, the main hallmarks of radiation-based imaging procedures, and minimum standard of image quality in various fields of radiology have been published in Europe, defining levels of performance considered necessary to produce images of standard quality for a particular anatomical region [18].

In computed tomography, quality criteria were initially addressed in European guidelines established in 1999 [19] and revised in 2004 [18]. Cardiac CTA was excluded from those reports, being at a relatively early stage of development at that time.

Similarly, no standards have been defined in the literature for performing ICA, and only a few proposals have been made to identify a set of common operative protocol criteria [20–22].

In the setting of a multicentre trial such as DISCHARGE, a standard of quality was considered required. For this purpose, the “10-steps guide to performing cardiac CT” [2] was established, and a general recommendation to perform ICA was given.

The aims of our study were dual:

- Evaluate the benefits of a pilot study on the adherence to these guides (general recommendation to perform ICA and the “10-steps guide to performing cardiac CT” [2]) and to increase internal validation of the DISCHARGE trial and therefore its external validation.
- Assess the effectiveness of the “10-steps guide to performing cardiac CT” [2] on image quality

Materials and methods

Ethical approval and study population

The DISCHARGE trial consortium (FP7/2007-2013, grant agreement EC-GA 603266) includes 25 clinical centres distributed in 16 European countries. Ethical approval for the non-randomised anonymised pilot study was obtained by the coordinating centre (Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, Freie Universität Berlin, Berlin, Germany) and by other clinical centres if locally required. To be considered for enrolment in the DISCHARGE trial, patients needed a referral to undergo CCTA or ICA for suspected coronary artery disease (CAD). The exclusion criteria were known CAD, age under 30 years, dialysis, known heart disease and pregnancy. The pilot study started on 1 April 2014 and ended on 31 December 2016.

Study design

For the non-randomised anonymised pilot study, each centre had to enrol 60 patients (30 for the CCTA arm and 30 for the ICA arm) and send 6 “high adherence” imaging datasets (3 CCTA and 3 ICA) to the core lab.

“High adherence” was defined as adherence to the exclusion/inclusion criteria of the pilot study and conformity to the CCTA protocol and ICA recommendations. Both CCTA protocols and ICA recommendations have been drafted by mixing core-lab/clinical sites inputs and existed literature and given to the sites before pilot study start.

The datasets were evaluated and approved by the core lab for high adherence, followed by an image quality assessment [2]. In case an imaging dataset was not approved, feedback was given by the core lab, and a new dataset was requested. This loop procedure was called a “round” and repeated until a total of 6 datasets (3 CCTA and 3 ICA) meeting the quality requirements were available from the respective centre (see Scheme 1.). Each “round” was formally considered concluded after a sent feedback was provided by the core lab to the site, regardless of the number of cases submitted (i.e. even less than 3). A round ended with the feedback given and not with the achievement of the requested number of datasets. The database containing the “high adherence” datasets was called the final accepted database (FADB).

For each imaging dataset, a data transmittal form had to be included with the following patient details: age, body mass index (BMI), weight, height, gender, heart rate during the scan and dose-length product (DLP).

Quality Assessment

CCTA protocol adherence

CCTA protocol adherence consisted of the rigid application to the inclusion/exclusion criteria of the pilot study and to the “10-steps guide to performing cardiac CT” as previously reported ².

Protocol deviations were analysed as follows (see Table 1 for a detailed checklist):

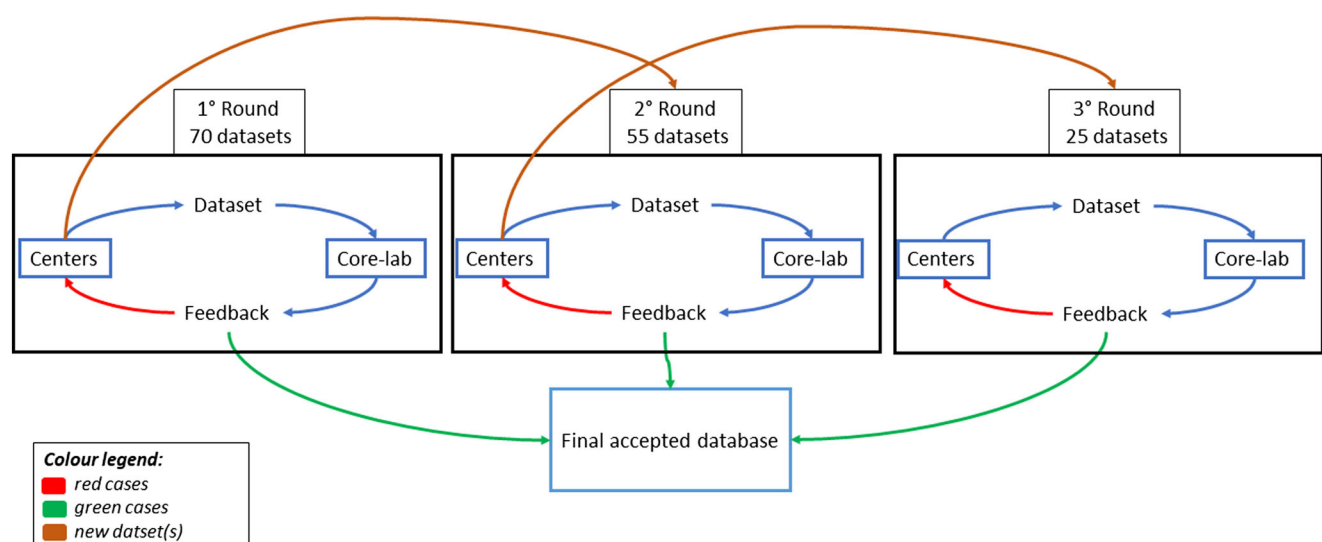
- Clinical ineligibility to the pilot study: general contraindications to the exam and presence of known CAD (shown by a stent or coronary artery bypass graft (CABG))
- Availability of all requested scans, namely coronary artery calcium score [CACS] and CTA plus an enlarged FOV reconstruction for evaluation of extra-cardiac findings (i.e. > 16 cm)
- Adherence to recommended scanning parameters including an established field of view, slice increment and slice thickness and reconstruction performed (iterative reconstruction and filtered back projection)

Protocol deviations were classified according to severity and categorised with a colour scale as minor (yellow), moderate (orange), and severe (red) (Table 2).

Protocol adherence was considered sufficiently respected for datasets without red errors (“high adherence” dataset).

For the per-dataset analysis, the colour assigned was that of the worst deviation; e.g. a case with one red error and 4 yellow ones was defined as red.

Dataset was categorized as green, in the presence of no errors.



Scheme 1 The “round” (black box) algorithm showing the flow of the study (arrows)

Table 1 Detailed quality criteria analysis of the all available CCTA datasets

General protocol part	Protocol adherence parameters	Number and percentage
Exclusion criteria ^a	Stent	3 (2%)
	Age < 30 years	1 (0.7%)
CACS scan	Performed	139 (92.7%)
	Scan length on the z-axis (< 16 cm)	126 (90.6%)
	Slice thickness (3 mm)	126 (90.6%)
	Slice increment (3 mm)	108 (77.7%)
	IR and FBP recon	47 (33.8%)
CCTA scan	FOV (< 20 cm)	129 (86.0%)
	Scan length on the z-axis has to be reduced by using CACS scan as a mask	120 (80.0%)
	Slice thickness (≤ 0.8 mm)	146 (97.3%)
	Slice increment (≤ 0.5 mm)	139 (92.7%)
	IR and FBP recon	57 (38.0%)
	Sharply coronary arteries visualization	133 (88.7%)
	Kidney not displayed	147 (98.0%)
	Aortic arch not displayed	149 (99.3%)
Non-cardiac structure scan	FOV (> 32 cm)	106 (70.7%)
	Slice thickness (1 mm)	103 (68.7%)
	Slice increment (1 mm)	98 (65.3%)
	Images based on CACS scan row data	84 (56%)
	Images based on CTA scan row data	121 (80.7%)
	IR and FBP recon ^o	46 (30.7%)

CACS, coronary artery calcium score; IR, iterative reconstruction; FBP, filtered back projection; CCTA, cardiac CT angiography; FOV, field of view

^a The exclusion criteria are 4: age < 30 years, pregnancy, dialysis, and known coronary artery disease (CAD).

^o Iterative and filtered back reconstruction should be provided for all acquisitions including CACS, CCTA, and non-cardiac structure retro-reconstruction

CCTA image evaluation

CCTA analysis was performed using a dedicated workstation (Vitrea fX, version 6.2, Vital Images). Images were evaluated qualitatively and quantitatively.

CCTA qualitative analysis

Qualitative image analysis was performed by two readers with different cardiac imaging experience (GDR with 4 years of

experience and MD with 15 years of experience) in consensus. Image quality was assessed using a Likert 5-point scale, as applied in previous studies (1 = non-diagnostic, 2 = poor, 3 = adequate, 4 = good and 5 = very good) [16, 23–28]. Image quality scores were assigned for overall image quality and separately for the left and right ventricle and each coronary segment. In addition, a score of 1 to 3 was assigned to the levocardigram, defined as selective enhancement of the left ventricular cavity [29]. A coronary arteries gap > 50%, were defined as NDX [30].

Table 2 Colour scale description

Errors	Definition
Red/critical	Known CAD; visualization of the kidney and/or the aortic arch; absence of lung recon based on CCTA or CACS scan; motion artefacts > 50%; scan length lower in CACS then in CCTA on the z-axis
Orange/major	CCTA FOV < 20 cm, slice thickness (≤ 0.8 mm) and slice increment (≤ 0.5 mm) in the CCTA scan and FOV (32 cm), slice thickness (≤ 1 mm) and slice increment (≤ 1 mm) in the non-cardiac structure scan
Yellow/minor	FOV < 20 cm in CACS scan, slice increment, and slice thickness of CACS scan (3 mm); missing of FBP and IR recon for CACS scan, CCTA scan and non-cardiac scan

CAD, coronary artery disease; CCTA, cardiac CT angiography; CACS, coronary artery calcium score; FOV, field of view; FBP, filtered back projection; IR, iterative reconstruction

CCTA quantitative analysis

For quantitative analysis, regions of interest (ROI) were placed (left ventricle, right ventricle, coronary segments numbers: 1, 2, 5, 6, and 11 [31]) for measurement of the following parameters: attenuation, noise (SD in the ROI), signal-to-noise ratio (SNR), fat density, general noise (SD of 1 cm² ROI in the aortic root), left ventricular (LV) wall density, contrast, contrast-to-noise ratio (CNR), signal-to-general-noise ratio, contrast with fat (density minus fat density), contrast to general noise ratio, and contrast with fat to general noise ratio [27, 28, 32–35] (see Table 3 for details). The quantitative levocardiographic effect was also calculated as the attenuation difference between the left and right ventricle.

ICA image evaluation

Red deviations were considered as non-compliance with the inclusion/exclusion criteria of the pilot study (shown by a stent, CABG). Overall image quality was assessed using a qualitative scale. In addition, we estimated the number of projections needed: at least two for right coronary artery and four for the left coronary artery including a “spider” projection.

Finally, when significant stenosis was diagnosed, according to the DISCHARGE management flow chart, a percutaneous transluminal coronary angioplasty (PTCA) [21] had to be performed and the procedural images sent to the core lab.

Statistical analysis

The normally distributed parameters were compared using an analysis of variance first. Normality was investigated using

graphical techniques such as histograms or boxplots due to the low power of tests for normality. Post hoc comparison was performed using Tukey’s method and the *t* test as appropriate. For the per-dataset analysis, we performed a multinomial logistic regression since we are dealing with a binary outcome in different categories. Impact of core-lab input was also assessed by analysing the round-to-round deviation rate analysis, which was analysed using multinomial regression. The qualitative scores between the three rounds and the initial dataset and the FADB were evaluated using multinomial regression. In addition, we compared the non-diagnostic (NDX) rate between the initial dataset and the FADB. These parameters were compared between the non-diagnostic group and the diagnostic group using T-Test. The results are presented as odds ratios together with a 95% confidence interval. Basically, this model shows how the probability of the respective category increases over time. Implicitly this model takes multiplicity into account. Thus, no further adjustment was performed. For qualitative data, the comparison was performed using logistic or multinomial regression and chi-square test as appropriate.

Statistical analysis was performed using MedCalc 15.8 (MedCalc Software) and R 3.4.1 (R Foundation). A level of $p < 0.05$ was deemed statistically significant.

Results

Study population

At the end of the pilot study, we collected and retrospectively analysed 226 datasets (150 CCTA and 76 ICA) for protocol

Table 3 Quantitative image quality evaluation of the complete database and final accepted database (FADB)

Parameters	Complete database Value (CI 95%) [Min/Max]	Complete FADB Value (CI 95%) (Min/Max)	Definition
Density	494.9 (478.9–512.5) [339.1/875.0]	467.8 (445.3–486.1) [266.0/872.5]	Signal strength
Noise	29.8 (27.7–32.0) [9.4/179.6]	29.4 (23.9–32.2) [11.5/66.3]	SD in the ROI
SNR	15.8 (14.8–18.7) [2.1/50.2]	14.2 (13.5–18.6) [7.3/49.1]	Signal-to-noise ratio
LV wall density	93.5 (90.4–100.8) [31.5/210.1]	91.6 (83.8–100.7) [36.1/191.2]	Myocardium density
Contrast	400.6 (385.2–418.6) [248.1/666.3]	381.9 (351.1–405.9) [189.3/690.4]	Contrast density
CNR	12.8 (12.2–14.8) [1.9/42.2]	12.1 (10.7–14.6) [4.9/41.1]	Contrast-to-noise ratio
General noise	32.8 (30.8–34.6) [7.3/233.8]	29.3 (25.4–33.5) [9.5/83.2]	SD in a cm ² ROI in the aortic root
Fat density	− 74.4 (− 77.4 to − 72.5) [− 115.3/− 30.8]	− 77.9 (− 82.8 to − 73.9) [− 111.1/− 17.6]	Lowest signal around the ROI
Signal-to-general-noise ratio	15.5 (14.0–16.8) [1.7/70.1]	16.5 (13.5–18.4) [6.5/59.6]	Image quality
Contrast with fat	579.1 (557.0–589.2) [379.0/937.3]	554.1 (516.7–571.0) [312.8/946.5]	Contrast
Contrast with the fat to general noise	17.9 (16.5–19.3) [2.1/78.3]	19.0 (15.8–21.5) [7.9/67.4]	Image quality
Levocardiographic effect	280.0 (259.2–296.3) [− 258.7/750.6]	278.6 (250.4–299.1) [− 258.7/726.7]	Selective enhance of the left ventricle

CI, confidence interval; SD, standard deviation; ROI, region of interest; SNR, signal-to-noise ratio; LV, left ventricle; CNR, contrast-to-noise ratio

Table 4 Patients' characteristics

Parameters	CCTA			ICA			<i>p</i> ^o
	Value	Min	Max	Value	Min	Max	
BMI	28 ± 4.3	17.5	38.7	27.5 ± 3.9	20.6	36.5	= 0.78
Gender (% male)	49%			60%			= 0.09
Weight	81.6 kg ± 15.1	46 kg	124 kg	79.3 kg ± 14.6	44.0 kg	113.0 kg	= 0.83
Height	1.7 m ± 0.1	1.51 m	1.93 m	1.71 m ± 0.08	1.5 m	1.8 m	= 0.35
Minimum HR during the scan	52.4 bpm ± 5.3	40 bpm	63 bpm				
Maximum HR during the scan	59.2 bpm ± 10.2	45 bpm	120 bpm				
Overall effective dose (mSv)	6.7 ± 4.5	0.5	22.9	5.9 ± 4.3	1.9	19.04	= 0.38
Time of exposure (min)				4.0 ± 3.5	1.0	13.0	

Effective dose was calculated from dose-length product for CCTA using a conversion factor of 0.014 and from dose area product for ICA using a conversion factor of 0.225 [36]

CCTA, cardiac CT angiography; ICA, invasive coronary angiography; BMI, body mass index; HR, heart rate; bpm, beats per minute

^o*t* test and chi-square were used for comparison as appropriate

adherence, image quality, and non-diagnostic rate. The characteristics of our population for both arms are shown in Table 4.

Quality assessment

CCTA protocol adherence

Some centres needed more than one round to obtain 6 “high adherence” dataset. Overall, 53 of the 70 CCTA datasets (75.7%) initially sent to the core lab did not fulfil the minimum adherence criteria (Table 2). At the end of the pilot study, this number decreased to 17 of 75 (22%; chi-square = 14.5, *df* = 1, *p* = 0.0001). The complete results are shown in Table 5 (Fig. 1).

In terms of error analysis through the rounds, we observed an increase in adherence to the “10-steps guide to performing cardiac CT” [2], which was most pronounced between the first and the other two rounds, with a reduction of red datasets. However, we observed an increment of orange and yellow

datasets, albeit this was due to fewer red ones (for details of the error analysis, see Table 5 and Fig. 2).

CCTA qualitative analysis

For the qualitative analysis aspect, the overall database score was 3.6 (FADB = 3.7) with a median of 4 but, among these, 25 of 150 datasets were considered non-diagnostic with a percentage of 16.7% (Figs. 3 and 4). Considering the distribution of the qualitative assessment, the multinomial logistic regression showed an odds ratio of 2.13 (CI 95% 1.57–2.88), 1.92 (CI 95% 1.36–2.72), and 1.81 (CI 95% 1.26; 2.58) for red, orange, yellow, and green cases, respectively (see Table 5 for further details). Although, between the initial dataset and the FADB, we observed an absolute reduction of non-diagnostic rate (15 of 70 vs 9 of 75, [21.4%] vs [12%]), this difference was not statistically significant (chi-squared = 1.94 *df* = 1, *p* = 0.163).

Table 5 Errors analysis (per-dataset and per-error) through the rounds

CCTA						ICA	
Per-dataset	First round ^o	Second round ^o	Third round ^o	FADB ^o	OR (95% confidence interval)	Per-dataset	Final database
Red	53 of 70 (75.7%)	25 of 55 (45.5%)	12 of 25 (48%)	17 of 75 (22.7%)		Inclusion criteria	2 of 76 (2.6%)
Orange	6 of 70 (8.6%)	16 of 55 (29%)	2 of 25 (8%)	27 of 75 (36%)	2.13 (1.57, 2.88)	Not enough projections	13 of 76 (17.1%)
Yellow	3 of 70 (4.3%)	11 of 55 (20%)	6 of 25 (24%)	19 of 75 (25.3%)	1.92 (1.36–2.72)		RC, 7/13 (53.8%)
Green	8 of 70 (11.4%)	3 of 55 (5.5%)	5 of 25 (20%)	12 of 75 (16.7%)	1.81 (1.26; 2.58)		LC, 4/13 (30.8%)
							LC and RC, 2/13 (15.4%)

CCTA, cardiac CT angiography; ICA, invasive coronary angiography; LC, left coronary; RC, right coronary; FADB, final accepted database

^oThe apparent discrepancy in number between the round was due to the round-feedback system, in fact, a round ended with the feedback given and not with the achievement of the requested number of datasets. In particular, between the 1st and 2nd and between the 3rd and the FADB, centers sent 2 and 5 “extra” datasets. The odds ratios (OR) show the results of the multinomial logistic regression together with the 95% confidence interval. These take the color 2 “red” as the reference category

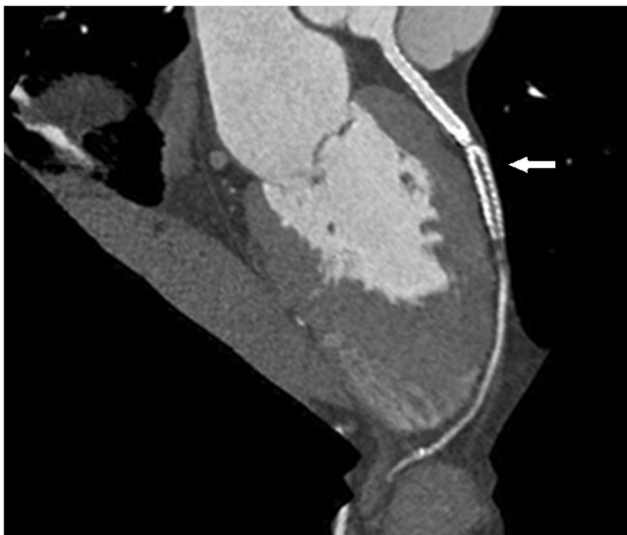


Fig. 1 Stents present in LAD. It is possible to identify 2 stents in the LAD (arrow) which is a violation of exclusion criteria

CCTA quantitative analysis

From the CCTA quantitative analysis point of view, for the completed database, the parameters are listed in Table 3. Regarding the FADB, the most notable were: SNR (14.2 CI 95% 13.5–18.6 ; max 49 and min 7.3), CNR (12.1 CI 95% 10.7–14.6); max 41.1 and min 4.9), signal-to-general-noise ratio (16.5 CI 95% 13.5–18.4; max 59.6 and min 6.3), and the contrast with the fat to general noise ratio (19.0 CI 95% 15.8–21.5 ; max 67.4 and min 7.9).

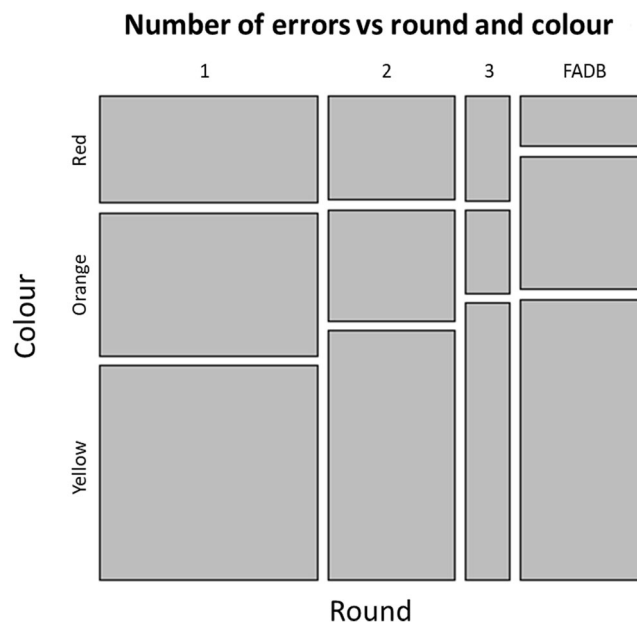


Fig. 2 Distribution of errors through the dataset. Plots of the different error distribution through the rounds

No statistically significant differences were found between the three rounds and the FADB, for all quantitative parameters taken into account (ANOVA $p > 0.05$ for each comparison).

Moreover, the image noise and general noise (SD in 1 cm² ROI in the aortic root) were significantly lower in the diagnostic cases group comparing with the non-diagnostic one (31.3 CI 95% 29.3–33.3 vs 39.8 CI 95% 25.7–53.9 [t test $p = 0.03$]; 32.7 CI 95% 29.8–34.6 vs 34.5 CI 95% 30.5–40.0 [t test $p = 0.01$], respectively).

ICA analysis

In the ICA arm, 2 cases were rejected due to not adhering to the exclusion criteria, because of the presence of a stent and a coronary artery bypass graft (2 of 76, 2.6%). Thirteen of 76 (17.1%) ICAs were rejected because of insufficient projections in the dataset analysed as follows: 4/13 (30.8%) cases for the left, 7/13 (53.8%) for the right and 2/13 (15.4%) ICAs for both coronary arteries. (Fig. 5).

Discussion

To ensure high-quality results, in DISCHARGE, an entire work package (WP3) has been addressed to quality criteria evaluation. In the CCTA arm, our assessment method moved from the more general European guidelines on quality criteria for computed tomography [18, 19] to more detailed methods that specifically focus on CCTA. In the ICA arm, we evaluated the adherence to the general recommendation on how to perform an ICA in the DISCHARGE trial, designed to strike with a balance between the number of projections and radiation risk, estimating a minimum of four projections for the left coronary arteries and two for the right one.

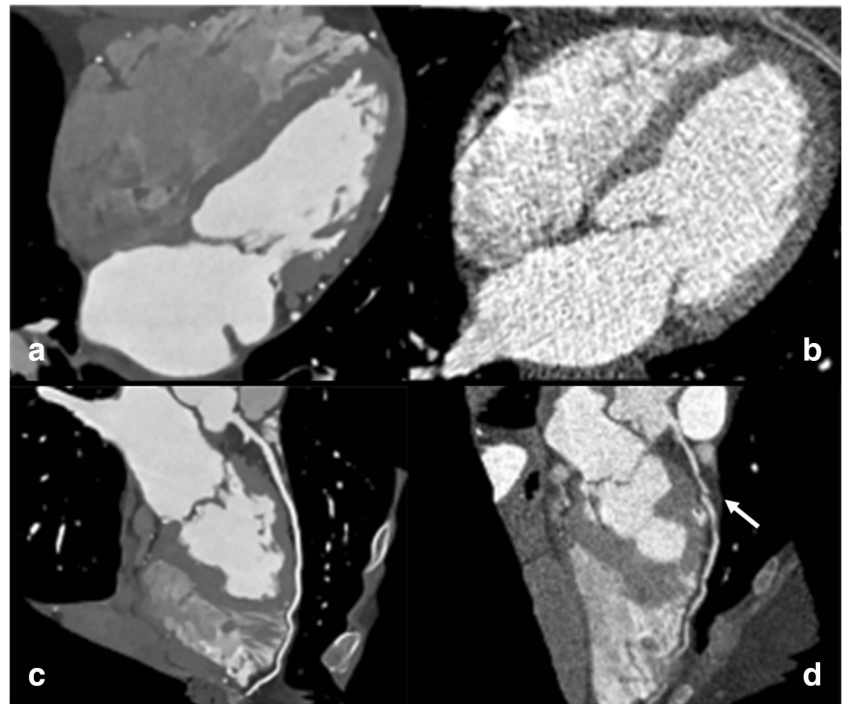
Major efforts were carried out by other research groups to define a standard protocol for CCTA [11, 12, 37]. Radiation dose reduction was the main focus of those reports, whereas image quality and NDX rate were only taken secondarily into account as indicators of protocol effectiveness.

This study meant to assess the impact of the DISCHARGE trial operative protocol (10-steps guide to performing cardiac CT) [2] on the predetermined protocol adherence, image quality, and NDX rate.

We also analysed the importance of the setting up of a dedicated core lab in the trial pilot study phase which resulted, in our experience, in a decrease of the NDX rate, an increase of adherence to protocol, and an improvement of image quality.

The CCTA NDX rate of the dataset initially sent to the core lab, was, unexpectedly, high (21.4%, 15 of 70) and, although it was reduced in the FADB (12%, 9 of 75), it remained elevated in comparison with the current literature. In fact, in a study from Gopal et al [38], with similar inclusion and

Fig. 3 Comparison between very good images and non-diagnostic (NDX) images. **a, b** Comparison between very good (5) and NDX (1) image quality in a 4-chamber view, image **a** shows a very high signal, low noise, high SNR, and high CNR; on the contrary, image **b** shows a poor signal, high noise, low SNR, and low CNR and demonstrates a poor levocardiographic effect defined as the selective opacification of the left chamber. **c, d** Comparison between very good and NDX images quality in the LAD; in addition, image **d** shows a gap in the LAD (arrow)



exclusion criteria, the CCTA NDX rate was 8% and Schuetz et al [39] in 2012, in a meta-analysis, showed as 9%. These data are even more important considering the high cardiac imaging experience of the centres involved in DISCHARGE. The high NDX rate and the lack of adherence at the beginning of the pilot study may reflect the intrinsic difficulties in fitting their well-established on-site protocol to the “10-steps guide to performing cardiac CT” [2].

Regarding the protocol adherence analysis, interestingly, the major unfulfilled aspect of the “10-steps guide to performing cardiac CT” [2] was the non-cardiac structure scan (see Table 1), leading to a potential missed diagnosis of non-cardiac findings; precisely, the possibility to detect the extra-cardiac findings is one of the important advantages of CCTA with respect to ICA [40]. Moreover, considering that the protocol adherence assessment was carried out only in a subset of images submitted by the centres, defined by them as “high adherence” cases, our initially high rate of CCTA that did

not fulfil the minimum adherence criteria (75.7%) was unexpected.

From an image quality point of view, our qualitative score moved from 3.6 in the initial dataset to 3.7 in the FADB, remaining still lower as compared to a study from Tatsugami et al (from 3.75 ± 0.38 to 4.24 ± 0.38) [25].

The SNR and the CNR of the FADB were 14.2 (CI 95% 13.5–18.6) and 12.1 (CI 95% 10.7–14.6) which are conversely considerably higher compared with a comparable analysis conducted by Tumor et al (SNR = from 10.47 ± 3.29 to 11.0 ± 3.63 ; CNR = from 8.33 ± 3.08 to 7.95 ± 2.68) [41]. In addition, signal-to-general-noise ratio and contrast with fat to general noise ratio are higher than Feger et al [32] (respectively, 16.5 (CI 95% 13.5–18.4) vs $9.4 \pm 3.0/12.6 \pm 4.4$; 19.0 (CI 95% 15.8–21.5) vs $11. \pm 3.1/15.3 \pm 4.7$, respectively). The standard deviation (SD) was larger, probably, due to the differences in terms of CT scanners used in our study.

Fig. 4 Same projection of RCA in different patients. **a, b** The same projection of RCA; the arrow shows the stair-steps artefact with a displacement > 50% rendering the segment non-diagnostic

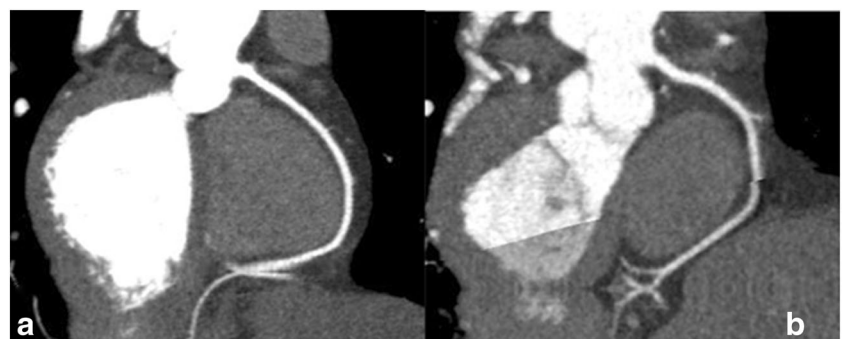
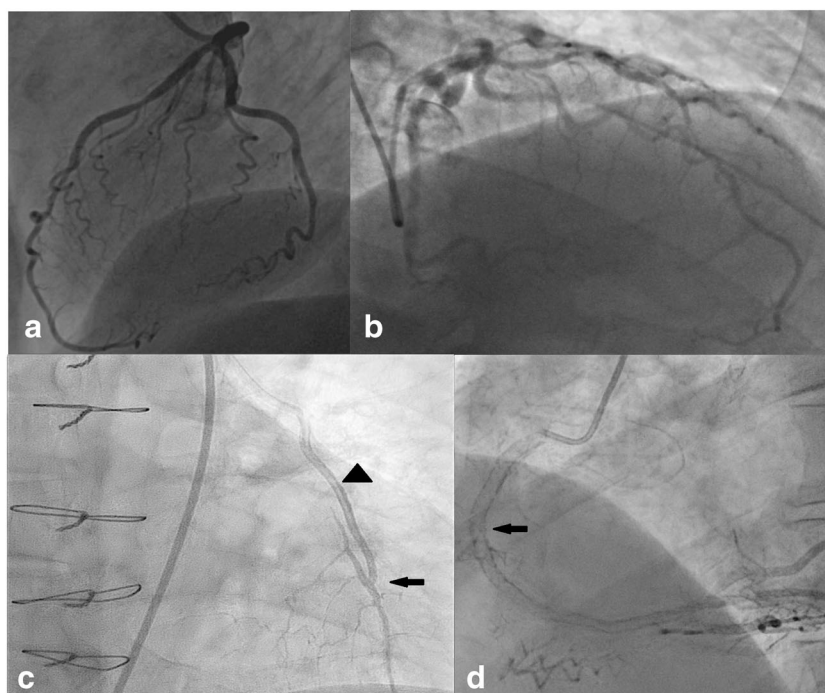


Fig. 5 ICA image quality and quality criteria evaluation. **a, b** Comparison between very good and poor (still diagnostic) ICA image quality; **c** The arrow shows the presence of a bypass graft (CABG) and the arrowhead shows the internal mammary artery; **d** The arrow shows the present of a stent in the RCA



Comparison between qualitative and quantitative assessment of image quality showed a significant discrepancy between evaluation methods, which has to be matched with the high prevalence of FADB NDX rate in our patient's cohort (12%). This asymmetry may lead to the assumption that, for more objective image quality evaluation, the qualitative analysis is the best approach.

Concerning the radiation dose analysis, our effective dose was $6.7 \text{ mSv} \pm 4.3$, which was higher than that of Rief et al [42] ($3.0 \text{ mSv} \pm 1.8$; 320-row scanner), but lower compared with that of Hausleiter et al [14] (12 mSv ; 64-row scanner). In our opinion, this difference is due to the large variability of technological equipment among the DISCHARGE consortium (ranging from 64-row scanner to the latest generation of dual-source CT); this hypothesis is supported by the relatively high value of SD obtained in our study.

The CCTA scientific literature interestingly lacks clinical studies specifically focusing on the evaluation of image quality in ICA, and those publications were based on purely qualitative methods [43, 44]. Whilst protocol standardization in Europe has been meticulously defined for x-ray-based diagnostic procedures [45] no specifications are reported concerning the minimum number of projections for ICA.

According to Smith et al [20], the optimal balance between radiation exposure and clinical yield was provided by three projections for the right coronary artery and four for the left coronary artery. Despite the DISCHARGE protocol being more focused on radiation safety, reducing to, at least, 2 projections for the right coronary arteries (RCA), 9 out of 76 (11.8%) ICA presented just one projection for the RCA.

Anyhow, our dosimetric data (fluoroscopy time $4.0 \text{ min} \pm 3.5$; effective dose $5.9 \text{ mSv} \pm 4.3$) reflect the existing literature, in fact in a review, Pantos et al [46] showed an average fluoroscopy time (6398 studies reported) 4.7 min (ranging $0.3\text{--}57 \text{ min}$) and an average effective dose (3418 studies reported) 9.1 mSv (ranging $0.3\text{--}15.8 \text{ mSv}$).

Our study has several potential limitations to be acknowledged.

First, the objective difficulty for the site to shift from their clinical routine protocol towards DISCHARGE standard operative procedure could explain this high non-compliance rate. This scheme proposal, however, may serve as an operative base for future clinical trials using cardiac CTA.

Second, there are obvious intrinsic limitations of a subjective qualitative image quality assessment, which is difficult to compare with similar studies and intrinsically biased by the arbitrariness of the score used, although it has been previously applied, however, by other investigators [47, 48].

Third, we did not define the set of cut-offs for each image quality quantitative parameter and, especially for CNR and SNR and further studies are necessary to define such cut-offs.

In summary, during the pilot study of DISCHARGE, we were able to decrease the CCTA NDX rate and improve the image quality and, therefore, we could consider the “10-steps guide to performing cardiac CT” [2] could be proposed as a standard operative protocol and EU cardiac CTA quality standard that should be adopted in further RCTs and in clinical practice.

In addition, this study shows that, despite the high grade of cardiac imaging specialisation [49], a pilot study before an

imaging randomised control trial (RCT) is helpful to define and to increase adherence to a common image acquisition protocol. This allows to build up a standard of quality both for ICA and for CCTA that is mandatory to increase internal consistency and external validation of the DISCHARGE trial.

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Methodology

- Prospective
- Observational/experimental
- Multicenter study

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Affiliations

Gianluca De Rubeis¹ · Adriane E. Napp² · Peter Schlattmann³ · Jacob Geleijns⁴ · Michael Laule⁵ · Henryk Dreger⁵ · Klaus Kofoed^{6,7} · Mathias Sørgaard⁷ · Thomas Engstrøm⁷ · Hans Henrik Tilsted⁷ · Alberto Boi⁸ · Michele Porcu⁹ · Stefano Cossa¹⁰ · José F. Rodríguez-Palomares¹¹ · Filipa Xavier Valente¹¹ · Albert Roque¹² · Gudrun Feuchtner¹³ · Fabian Plank¹⁴ · Cyril Štěchovský¹⁵ · Theodor Adla¹⁶ · Stephen Schroeder¹⁷ · Thomas Zelesny¹⁸ · Matthias Gutberlet¹⁹ · Michael Woinke²⁰ · Mihály Károlyi²¹ · Júlia Karády²² · Patrick Donnelly²² · Peter Ball²³ · Jonathan Dodd²⁴ · Mark Hensey²⁵ · Massimo Mancione²⁶ · Andrea Ceccacci²⁶ · Marina Berzina²⁷ · Ligita Zvaigzne²⁸ · Gintare Sakalyte²⁹ · Algidas Basevičius³⁰ · Małgorzata Ilnicka-Suckiel³¹ · Donata Kuśmierz³² · Rita Faria³³ · Vasco Gama-Ribeiro³³ · Imre Benedek³⁴ · Teodora Benedek³⁴ · Filip Adjić³⁵ · Milenko Čanković³⁶ · Colin Berry³⁷ · Christian Delles³⁷ · Erica Thwaite³⁸ · Gershon Davis³⁹ · Juhani Knuuti⁴⁰ · Mikko Pietilä⁴¹ · Cezary Kepka⁴² · Mariusz Kruk⁴³ · Radosav Vidakovic⁴⁴ · Aleksandar N. Neskovic⁴⁴ · Iñigo Lecumberri⁴⁵ · Ignacio Diez Gonzales⁴⁶ · Balazs Ruzsics⁴⁷ · Mike Fisher⁴⁷ · Marc Dewey² · Marco Francone^{1,48}  · The DISCHARGE Trial Group

¹ Department of Radiology, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy

² Department of Radiology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

³ Department of Statistics, Informatics and Data Science, Jena University Hospital, Jena, Germany

⁴ Department of Radiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

⁵ Department of Cardiology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

⁶ Department of Radiology, Rigshospitalet Region Hovedstaden, Rigshospitalet 9, 2100 Copenhagen, Denmark

⁷ Department of Cardiology, Rigshospitalet Region Hovedstaden, Rigshospitalet 9, 2100 Copenhagen, Denmark

⁸ Department of Cardiology, Azienda Ospedaliera Brotzu, Cagliari, CA, Italy

⁹ Department of Radiology, Azienda Ospedaliera Universitaria di Cagliari, AOU di Cagliari - Polo di Monserrato, 09042 Monserrato, CA, Italy

¹⁰ Department of Radiology, Azienda Ospedaliera Brotzu, Cagliari, CA, Italy

¹¹ Department of Cardiology, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Passeig de Vall d'Hebron 119, 08035 Barcelona, Spain

- ¹² Department of Radiology, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Passeig de Vall d'Hebron 119, 08035 Barcelona, Spain
- ¹³ Department of Radiology, Medical University Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria
- ¹⁴ Department of Cardiology, Medical University Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria
- ¹⁵ Department of Cardiology, University Hospital Motol, Vůvalu 84, 150 06 Prague 5, Czech Republic
- ¹⁶ Department of Radiology, University Hospital Motol, Vůvalu 84, 150 06 Prague 5, Czech Republic
- ¹⁷ Department of Cardiology, ALB FILS KLINIKEN GmbH, Eichertstrasse 3, 73035 Goeppingen, Germany
- ¹⁸ Department of Radiology, ALB FILS KLINIKEN GmbH, Eichertstrasse 3, 73035 Goeppingen, Germany
- ¹⁹ Department of Radiology, University of Leipzig Heart Centre, Strümpellstrasse 39, 04289 Leipzig, Germany
- ²⁰ Department of Cardiology, University of Leipzig Heart Centre, Strümpellstrasse 39, 04289 Leipzig, Germany
- ²¹ MTA-SE Cardiovascular Imaging Center, Heart and Vascular Center, Semmelweis University, Varosmajor u 68, Budapest 1122, Hungary
- ²² Department of Cardiology, Southeastern Health and Social Care Trust, Upper Newtownards Road Ulster, Belfast BT16 1RH, UK
- ²³ Department of Radiology, Southeastern Health and Social Care Trust, Upper Newtownards Road Ulster, Belfast BT16 1RH, UK
- ²⁴ Department of Radiology, St. Vincent's University Hospital and National University of Ireland, Belfield Campus, 4, Dublin, Ireland
- ²⁵ Department of Cardiology, St. Vincent's University Hospital, Belfield Campus, 4, Dublin, Ireland
- ²⁶ Department of Cardiovascular, Respiratory, Nephrology, Anesthesiology and Geriatric Sciences, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy
- ²⁷ Department of Cardiology, Paul Stradins Clinical University Hospital, Pilsoņu Street 13, Riga 1002, Latvia
- ²⁸ Department of Radiology, Paul Stradins Clinical University Hospital, Pilsoņu Street 13, Riga 1002, Latvia
- ²⁹ Department of Cardiology, Lithuanian University of Health Sciences, Eivėlniu 2, 50009 Kaunas, Lithuania
- ³⁰ Department of Radiology, Lithuanian University of Health Sciences, Eivėlniu 2, 50009 Kaunas, Lithuania
- ³¹ Department of Cardiology, Wojewodzki Szpital Specjalistyczny We Wrocławiu, Ul. Henryka Michala Kamińskiego, 51124 Wrocław, Poland
- ³² Department of Radiology, Wojewodzki Szpital Specjalistyczny We Wrocławiu, Ul. Henryka Michala Kamińskiego, 51124 Wrocław, Poland
- ³³ Department of Cardiology, Centro Hospitalar de Vila Nova de Gaia, Rua Conceicao Fernandes, 4434 502 Vila Nova de Gaia, Portugal
- ³⁴ Department of Cardiology, Cardio Med Medical Center, 22 decembrie 1989, 540156 Targu-Mures, Romania
- ³⁵ Radiology Department Imaging Center, Institute of Cardiovascular Diseases of Vojvodina, Put dr Goldmana 4, Sremska Kamenica, Novi Sad 212014, Serbia
- ³⁶ Department of Cardiology, Institute of Cardiovascular Diseases of Vojvodina, Put dr Goldmana 4, Sremska Kamenica, Novi Sad 212014, Serbia
- ³⁷ Institute of Cardiovascular and Medical Sciences, University of Glasgow, University Place 126, Glasgow G12 8TA, UK
- ³⁸ Department of Radiology, Aintree University Hospital, Longmoor Lane, Liverpool L9 7AL, UK
- ³⁹ Department of Cardiology, Aintree University Hospital, Longmoor Lane, Liverpool L9 7AL, UK
- ⁴⁰ Turku PET Centre, Turku University Hospital and University of Turku, Kiinamyllynkatu 4-8, 20120 Turku, Finland
- ⁴¹ Heart Centre, Turku University Hospital, Kiinamyllynkatu 4-8, FI 20120 Turku, Finland
- ⁴² Department of Radiology, The Institute of Cardiology in Warsaw, Ul. Alpejska 42, 04-628 Warsaw, Poland
- ⁴³ Department of Cardiology, The Institute of Cardiology in Warsaw, Ul. Alpejska 42, 04-628 Warsaw, Poland
- ⁴⁴ Department of Cardiology, Clinical Hospital Center Zemun, Vukova 9, Belgrade-Zemun 11080, Serbia
- ⁴⁵ Department of Radiology, Basurto University Hospital, Avenida Montevideo 18, 48013 Bilbao, Spain
- ⁴⁶ Department of Cardiology, Basurto University Hospital, Avenida Montevideo 18, 48013 Bilbao, Spain
- ⁴⁷ Department of Cardiology, Royal Liverpool and Broadgreen University Hospitals, Prescott Street, Liverpool L7 8XP, UK
- ⁴⁸ Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, V.le Regina Elena, 324 00161 Rome, Italy