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Italian multicenter, prospective study to evaluate the negative predictive value of 16- and 64-slice MDCT imaging in patients scheduled for coronary angiography (NIMISCAD-Non Invasive Multicenter Italian Study *for* Coronary Artery Disease)

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Abstract This was a prospective, multicenter study designed to evaluate the utility of MDCT in the diagnosis of coronary artery disease (CAD) in patients scheduled for elective coronary angiography (CA) using different MDCT systems from different manufacturers. Twenty national sites prospectively enrolled 367 patients between July 2004 and June 2006. Computed tomography (CT) was performed using a standardized/optimized scan protocol for each type

Table 1 Main technical and scan parameters of the CT systems and number of studied patients

CT system	Rot. T (ms)	TR (ms)	ST (mm)	Patients (N=350)
GE *Lightspeed16^pro*	400	200	16×0.625	108
Siemens *Sensation16*	375	188	16×0.75	95
Philips *Brilliance16*	420	210	16×0.75	41
Toshiba *Aquilon16*	400	200	16×0.5	40
GE *Volume CT*	350	175	64×0.625	20
Siemens *Sensation64*	330	165	32×2×0.6	29
Philips *Brilliance64*	400	200	64×0.625	12
Toshiba *Aquilon64*	400	200	64×0.5	5

Rot. T = rotation time, TR = temporal resolution, ST = slice thickness

All images were reconstructed in all phases of the entire cardiac cycle, by means of retrospective synchronization with the ECG track, expressed as a percentage of the R-R interval (relative delay) or as absolute temporal distance (ms) before the next R wave.

MDCT angiographic analysis

MDCT angiograms were analyzed both on-site and off-site. The on-site analysis was conducted by a single radiologist at each center who was aware of the patient's clinical condition, but blinded to the results of the invasive CA. Among the data sets reconstructed at several phases of the cardiac cycle, the three with the best image quality were saved on CD and sent for centralized off-site evaluation that was performed by two independent radiologists with proven experience in cardiac CT imaging, but who were not involved in the clinical study and who were blinded to any patient-related information. Any disagreement between off-site readers was resolved by consensus. An evaluating form with coronary arteries segmented according to the guidelines of the American Heart Association (AHA) [5] was used for both analyses. Lesions were classified by the maximal luminal diameter stenosis by qualitative analysis of the most severe well-defined lesion in each segment. Segments were classified as normal (smooth, parallel, or tapering borders), as non-significant disease (luminal irregularities or <50% lumen reduction), as significant stenoses (lumen reduction between 50% and 99%), or occluded. In the case of multiple lesions in a given segment, the segment was classified by the worst lesion. In the case of multiple abnormal segments per artery, the vessel was classified by the worst segment. Patients were classified as positive for the presence of significant CAD if there was at least one stenosis >50%.

Invasive angiographic analysis

CA was performed by standard techniques within 2 weeks after MDCT procedure, using a transfemoral or transradial technique. CA was evaluated on-site by a single experienced cardiologist blinded to the MDCT findings. Segmental disease was analyzed in each vessel using the same 15-segment model and form employed for MDCT analysis. Stenosis severity in each segment was classified according to the maximal luminal diameter stenosis present in each segment. Lesions were examined in orthogonal views and stenosis severity quantitatively determined using an automated edge detection system (quantitative CA, QCA).

Data analysis

The assessment of MDCT accuracy was performed according to a per-patient on-site and off-site evaluation; an on-site artery- and segment-based approach analysis was also performed.

The per-patient analysis included all eligible patients, except those negative at MDCT with at least one of the following segments not assessable at MDCT: 1, 2, 3, 5, 6, 7, 8, 9, 11, and 13. A patient was classified as true positive if at least one significant coronary stenosis (>50% or occlusion) detected by both modalities was present, regardless of location; a patient was considered as true negative if no significant lesion was found by both modalities.

In the per-artery analysis, segments were combined as right coronary artery (RCA: 1, 2, 3), left main artery (LMA: 5), anterior descending artery (ADA: 6, 7, 8, 9), and circumflex artery (CXA: 11, 13). Arteries deemed negative at MDCT, but with at least one non-assessable segment were excluded. An artery was classified as true positive if at least one significant lesion was detected by both investigations, regardless of location and irrespective of whether or not it was considered for patient inclusion; true-negative arteries appeared normal on all assessable and negative segments.

The per-segment analysis included only segments that were assessable on both investigations. True positives were defined as correct identification by MDCT of significant coronary artery stenosis and true negatives were defined as correct identification by MDCT of segments with stenosis of 50% or less.

Once the concordance of the MDCT with the reference standard had been assessed, the following statistics were calculated: sensitivity, specificity, NPV, positive predictive value (PPV), and diagnostic accuracy (DA).

The primary analysis was the evaluation of the NPV on a per-patient basis, obtained both in on-site and off-site evaluation. Expecting a prevalence of CAD ranging from 0.50 to 0.70, and a specificity of 0.95, the NPV was a

function of the sensitivity. Since no precise data were available for this parameter, the sample size was calculated in order to obtain a 95% confidence interval for the estimate of sensitivity of not more than 0.1, with the lower limit >0.80. The required number of evaluable patients varied from 254 (prevalence 0.70) to 392 (prevalence 0.50). Anticipating a 10% drop-out rate, it was considered necessary to enroll between 280 and 431 subjects. After the enrollment of about 200 patients, an interim analysis was foreseen in order to obtain a more precise estimate of the prevalence of the disease in the sample studied. Based on the analysis results, a recalculation of the necessary number of subjects was performed.

Secondary analyses included the on-site evaluation on a per-artery and per-segment basis. Furthermore, the on-site per-patient analysis was also conducted in subgroups defined by the National Cholesterol Education Program (NCEP) coronary heart disease (CHD) risk (low, intermediate, high) [6], by BMI (<25 kg/m^2, 25–30 kg/m^2, >30 kg/m^2), calcium score (<100, 101–400, 401–$1,000$, $>1,000$ AS), and type of MDCT scanner (16- and 64-slice). A χ^2 test for trend was used to test for differences in the modality results in different subgroups of patients. Secondary analysis also included a safety assessment reporting the occurrence of adverse events. Results are expressed as point estimates and their exact 95% confidence intervals (95% CIs). All p-values are two-tailed. Analyses were carried out using SAS System Version 8.20 (SAS, Cary, NC).

Results

Between July 2004 and June 2006, a total of 367 patients scheduled for elective CA for suspected CAD at 20 Italian centers were screened. Seventeen patients (5%) were subsequently excluded due to: CA erased (n=1), major protocol violation (n=9), temporary MDCT equipment unavailability (n=5), and patient refusal (n=2). The final study sample included 350 eligible patients.

Academic institutions comprised 60% of the centers: 35% were located in northern Italy, 45% in central Italy, and 20% in southern Italy and the islands. Both the type and geographical distribution of the institutions were well distributed and representative of the national situation. Figure 1 shows the trial flow diagram and details of reasons for patient ineligibility. A total of 284 (81%) patients were scanned by a 16-slice MDCT scanner, while the remaining 66 (19%) by a 64-slice MDCT. The characteristics of the 350 eligible patients are summarized in Table 2.

Per-patient analyses

Results of the per-patient analyses are reported in Table 3. Out of 295 patients analyzed in the off-site evaluation, 166 had at least one segment with a stenosis >50% by QCA, which translates into a disease prevalence of 56%. NPV of MDCT was 0.73 (95% CI 0.65–0.79) and PPV was 0.93 (95% CI 0.87–0.97). Sensitivity was 0.73 (95% CI 0.65–0.79), specificity was 0.93 (95% CI 0.87–0.97), and DA was 0.82 (95% CI 0.77–0.86).

The on-site evaluation included 327 patients with a CAD prevalence of 58%. NPV of MDCT was 0.91 (95% CI 0.85–0.95), and PPV was 0.91 (95% CI 0.86–0.95). Sensitivity was 0.94 (95% CI 0.89–0.97), specificity was 0.88 (95% CI 0.81–0.93), and DA was 0.91 (95% CI 0.88–0.94).

Evaluating the CHD risk in our population, the prevalence was 0.38 for the low risk, 0.65 for the intermediate risk, and 0.77 for the high risk. Although non-statistically significant, there was evidence in favor of a trend of
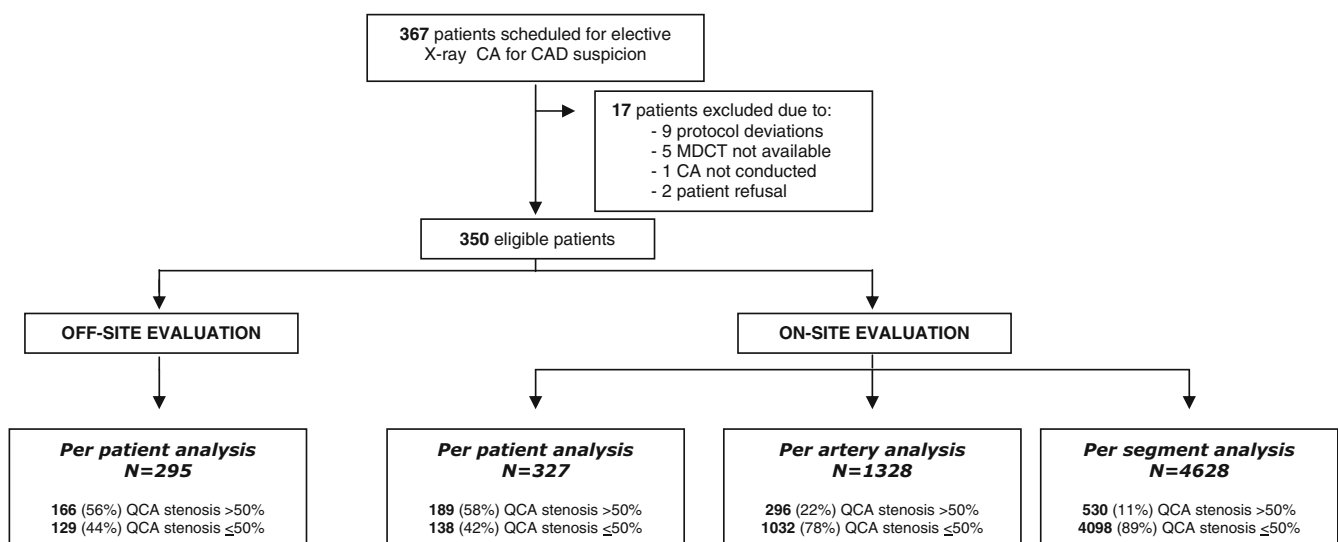

Fig. 1 Study flow chart

Table 2 Patient characteristics, n (%)

Eligible patients	350
Age[1] - years	64.0 (19–83)
Male	265 (75.7)
BMI- kg/m^2	
<25	110 (31.4)
25–30$^-$	193 (55.1)
≥30	47 (13.4)
Total cholesterol[1] - mg/dl	201.3 (95–347)
HDL[1] - mg/dl	49 (22–99)
SBP - mmHg	130.0 (95–210)
DBP - mmHg	80.0 (60–100)
HR- beat/min	64.0 (35–100)
Current smoking habit	113 (32.3)
NCEP CHD risk	
Low	124 (35.4)
Intermediate	167 (47.7)
Peripheral disease	59 (16.9)
Statin treatment	140 (40.0)
Diabetes	87 (24.9)
Beta-blocker treatment	128 (36.6)
Agatston Calcium Score	
0–100	168 (48)
101–400	90 (25.7)
401–1,000	44 (12.6)
>1,000	48 (13.8)

[1]Median (range)
BMI = Body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; NCEP = National Cholesterol Education Program; CHD = coronary heart disease

decreasing NPV with increasing CHD risk: 0.93 in low risk and 0.79 in high risk patients (χ^2 test for trend=2.11; p= 0.147). No differences in DA were observed.

Assessing the influence of BMI on MDCT performance, false-positive results were more frequent in obese patients, specificity fell from 0.92 in normal patients to 0.67 in obese subjects (χ^2 test for trend=6.29; p=0.012). PPV was slightly negatively affected by BMI: 0.92 in normal and 0.76 in obese subjects (χ^2 test for trend=4.00; p=0.046). Non-significant differences resulted for sensitivity, NPV, and DA because of a high number of correct negatives (14/21).

The analysis of calcium score effect was performed by collapsing the two higher categories (401–1,000 and >1,000 AS) into one, because of the low number of patients in each category. Specificity significantly (p<0.001) decreased when CACS increased: 0.94 (0–100 AS), 0.76 (101–400 AS), and 0.50 (>400 AS). NPV was negatively affected by increasing CACS: 0.94 (0–100 AS) vs. 0.86 (101–400 AS) vs. 0.62 (>400 AS). No effect on MDCT performance was observed for the type of CT machine.

On-site per-artery analysis

Results of the per-artery analysis are reported in Table 4. Of the 1,328 arteries analyzed on-site, 296 (22%) had a stenosis >50% by CA. NPV of MDCT was 0.96 (95% CI 0.93–0.98) for RCA, 0.99 (95% CI 0.97–1.00) for LMA, 0.91 (95% CI 0.86–0.95) for ADA, and 0.94 (95% CI 0.90–0.96) for CXA, respectively, with an overall NPV of 0.96 (95% CI 0.94–0.97).

On-site per-segment analysis

Results of the per-segment analysis are reported in Table 5. Of 4,628 segments analyzed on-site, 530 (11%) had a stenosis >50% by CA. The assessable segments were 3,746 (77.59%) by using the 16-slice MDCT system and 882 (78.61%) by using the 64-slice MDCT machine. NPV of MDCT was 0.96 (95% CI 0.95–0.97), and PPV was 0.72 (95% CI 0.68–0.76). Sensitivity was 0.70 (95% CI 0.66–0.74), specificity was 0.96 (95% CI 0.96–0.97), and DA was 0.93 (95% CI 0.93–0.94).

The overall image quality resulted in good (moderate and/or excellent) in 4,292 (93.95%) segments in the on-site analysis and in 3,396 (80.17%) segments in the off-site analysis.

Safety

Six adverse events related to MDCT occurred in 6/350 patients (1.7%): four cases of cutaneous rash, one case of vomiting, and one case of nausea. All cases were related to contrast medium injection, all completely recovered, and none was considered serious.

Discussion

Since the first reports [7, 8], MDCT has been characterized by continuous and rapid technical evolution, making it possible to examine the heart and the whole course of coronary arteries reliably within a single breath-hold, within a few heart beats, and with sub-millimeter spatial resolution. Many single-center experiences have been reported [9–28] using different MDCT technologies, most of which have been characterized by high values of DA in the assessment of patients scheduled for CA [9–18; 20–28]. On a per-patient basis, the average weighted sensitivity reported in these series for the detection of at least one coronary artery with >50% lumen stenosis is 94% (range 75% to 100%), whereas the average specificity is 77% (range 49% to 100%) [29–30]. In most of these studies using 16-slice MDCT, up to 23% of coronary segments were considered not assessable [19]; similarly, data analysis from 64-slice MDCT studies could not be

Table 3 Per patient analysis

Evaluation	N	Prevalence	Sensitivity	Specificity	PPV	NPV	DA
Off-site							
Overall	295	0.56	0.73 (0.65–0.79)	0.93 (0.87–0.97)	0.93 (0.87–0.97)	0.73 (0.65–0.79)	0.82 (0.77–0.86)
On-site							
Overall	327	0.58	0.94 (0.89–0.97)	0.88 (0.81–0.93)	0.91 (0.86–0.95)	0.91 (0.85–0.95)	0.91 (0.88–0.94)
By NCEP CHD risk							
Low	115	0.38	0.89 (0.75–0.96)	0.93 (0.84–0.98)	0.89 (0.75–0.96)	0.93 (0.84–0.98)	0.91 (0.85–0.96)
Intermediate	156	0.65	0.96 (0.90–0.99)	0.81 (0.69–0.91)	0.91 (0.84–0.95)	0.92 (0.80–0.98)	0.91 (0.85–0.95)
High	56	0.77	0.93 (0.81–0.99)	0.85 (0.55–0.98)	0.95 (0.84–0.99)	0.79 (0.49–0.95)	0.91 (0.80–0.97)
	χ^2 test for trend		$\chi^2=7.21;p=0.396$	$\chi^2=2.84;p=0.092$	$\chi^2=1.15;p=0.283$	$\chi^2=2.11;p=0.147$	$\chi^2=0.00;p=0.945$
By BMI							
<25 kg/m^2	102	0.50	0.94 (0.84–0.99)	0.92 (0.81–0.98)	0.92 (0.81–0.98)	0.94 (0.83–0.99)	0.93 (0.86–0.97)
25–30	181	0.63	0.93 (0.87–0.97)	0.91 (0.81–0.97)	0.95 (0.89–0.98)	0.88 (0.78–0.95)	0.92 (0.87–0.96)
≥30	44	0.52	0.96 (0.78–1.00)	0.67 (0.43–0.85)	0.76 (0.56–0.90)	0.93 (0.68–1.00)	0.82 (0.67–0.92)
	χ^2 test for trend		$\chi^2=0.01;p=0.913$	$\chi^2=6.29;p=0.012$	$\chi^2=4.00;p=0.046$	$\chi^2=0.29;p=0.590$	$\chi^2=3.43;p=0.064$
By calcium score							
0–100	151	0.32	0.88 (0.75–0.95)	0.94 (0.88–0.98)	0.88 (0.75–0.95)	0.94 (0.88–0.98)	0.92 (0.87–0.96)
101–400	86	0.71	0.95 (0.86–0.99)	0.76 (0.55–0.91)	0.91 (0.81–0.96)	0.86 (0.65–0.97)	0.90 (0.81–0.95)
>400	90	0.89	0.96 (0.89–0.99)	0.50 (0.19–0.81)	0.94 (0.86–0.98)	0.62 (0.24–0.92)	0.91 (0.83–0.96)
	χ^2 test for trend		$\chi^2=3.46;p=0.063$	$\chi^2=20.0;p<0.001$	$\chi^2=1.59;p=0.208$	$\chi^2=8.70;p=0.003$	$\chi^2=1.47;p=0.225$
By multidetector							
16-slice	264	0.58	0.94 (0.89–0.97)	0.86 (0.79–0.92)	0.91 (0.85–0.95)	0.91 (0.84–0.96)	0.91 (0.87–0.94)
64-slice	63	0.57	0.92 (0.78–0.98)	0.93 (0.76–0.99)	0.94 (0.81–0.99)	0.89 (0.72–0.98)	0.92 (0.82–0.97)
	χ^2 test		$\chi^2=2.93;p=0.588$	$\chi^2=0.74;p=0.388$	$\chi^2=4.94;p=0.482$	$\chi^2=1.23;p=0.726$	$\chi^2=0.08;p=0.772$

performed in all coronary segments, with a reported percentage of non-assessable segments of up to 12% [22, 26–28]. In a recent meta-analysis [31], it was demonstrated that NPV was sufficiently high with 16-section CT (92%), making this an excellent tool to rule out CAD, strengthening our choice to include centers with CT technology ≥16-slice MDCT. Before extensive clinical application of MDCT for CAD assessment can be advocated, it is necessary to establish whether or not the reported DA can be replicated in clinical practice in different centers with varying expertise

and MDCT manufacturer. In fact, the main limitations of the current data are the strict eligibility criteria used for patient selection, the restriction of high image-quality data sets to selected cohorts or subgroups of patients, and the predominance of a single MDCT manufacturer.

We conducted a prospective national multicenter study, reflecting the technical aspects of different MDCT systems (≥16-slice MDCT) available in Italy at the time of the study to determine whether MDCT can replace the invasive procedure in patients scheduled for elective CA in order to

Table 4 Per artery analysis by on-site evaluation

Artery	N	Prevalence	Sensitivity	Specificity	PPV	NPV	DA
RCA	322	0.28	0.90 (0.82–0.95)	0.92 (0.88–0.95)	0.82 (0.73–0.89)	0.96 (0.93–0.98)	0.92 (0.88–0.94)
LMA	346	0.03	0.75 (0.43–0.95)	0.99 (0.97–1.00)	0.69 (0.39–0.91)	0.99 (0.97–1.00)	0.98 (0.96–0.99)
ADA	334	0.42	0.88 (0.81–0.93)	0.89 (0.83–0.93)	0.85 (0.78–0.90)	0.91 (0.86–0.95)	0.88 (0.84–0.92)
CXA	326	0.17	0.69 (0.55–0.81)	0.95 (0.92–0.97)	0.75 (0.60–0.86)	0.94 (0.90–0.96)	0.91 (0.87–0.94)

Table 5 Per segment analysis by on-site evaluation

N	Prevalence	Sensitivity	Specificity	PPV	NPV	DA
4,628	0.11	0.70 (0.66–0.74)	0.96 (0.96–0.97)	0.72 (0.68–0.76)	0.96 (0.95–0.97)	0.93 (0.93–0.94)

exclude the presence of significant CAD. Bearing in mind that relevant coronary segments are essentially those suitable for a mechanical (PTCA/stenting) or surgical (CABG) treatment (diameter ≥1.5–2 mm), our study provides a per-patient on-site analysis of sufficiently high sensitivity (94%) and NPV (91%) of ECG-gated MDCT coronary angiography to rule out significant stenosis in patients scheduled for an elective CA in a large population. Our study confirms the role of MDCT coronary angiography for reliably excluding significant CAD in patients with an equivocal clinical presentation, with uninterpretable or equivocal stress-test results, or at low or intermediate risk for CAD. We found that a negative evaluable MDCT study could have avoided CA in 120/295 (41%) patients in the off-site evaluation and in 121/327 (37%) patients in the on-site assessment.

To the best of our knowledge, this is the first study in which patients were studied in several independent national centers with different expertise, using different MDCT machines from different manufacturers, with a standardized and optimized CT protocol. Only one similar multicenter study has been published to date [32]. In that report, 187 patients were studied in 11 participating sites, all using the same MDCT manufacturer. All MDCT and CA results were assessed by a single core laboratory in each case. The per-patient approach was characterized by sensitivity, specificity, PPV, and NPV of 75%, 77%, 60%, and 87%, respectively.

The difference between on-site and off-site evaluation in our study could, in part, be explained by the intrinsic characteristics of the latter assessment as well as by the fact that the two off-site readers were completely unaware of the patient's clinical information. It could also be because blinded assessment of each MDCT was performed by using only three data sets considered to be those with the best image quality by the on-site reader. These results were obtained in patients scheduled for elective CA and with a wide spectrum of clinical settings. The on-site specificity was somewhat lower in comparison with most of the published reports [9–28]. This is because there was a tendency to overestimate the severity of a lesion on CT (resulting in a number of false-positive outcomes) rather than underestimating the lesion severity and thereby "missing" lesions, which may have had serious consequences in a symptomatic patient population.

The clinical worldwide acceptance of MDCT coronary angiography will probably require further technological development to ensure optimal test results and a guiding management of CAD. The extension of MDCT system usage with higher temporal resolution (<100 ms) may extend the application of this technology for the assessment of CAD in a high probability pre-test population with extensive calcifications and without heart rate control [33–36]. The employment of hybrid PET/MDCT [37] or SPECT/MDCT equipment with image fusion [38] may offer the opportunity for a comprehensive non-invasive evaluation of the presence of CAD and its consequences, both in the coronary arteries and myocardium.

The radiation dose can be considered a limitation of this technique [39]; however, due to the study design, the dose analysis was not an objective of our study. The most effective method to reduce radiation exposure is the prospective ECG tube modulation (ECG pulsing) [40]. For 64-slice MDCT, this has been reported to be 14.8±1.8 mSv and 9.4±1.0 mSv without and with ECG-triggering tube output modulation, respectively, and for 16-slice MDCT, 10.6±1.2 mSv, and 6.4±0.9 mSv without and with ECG triggering tube output modulation, respectively [41].

Leading single center experience, with limited and selected patient populations often including patients who had previously undergone angiography, may be difficult to translate into general clinical practice. The multicenter study reported here should reflect the clinical value of MDCT coronary angiography more accurately, because a larger number of patients at different national centers has been evaluated using all the principal MDCT manufacturers, thus reflecting real-world clinical practice. The high NPV observed suggests that ECG-gated MDCT coronary angiography could be useful to discriminate those patients who really need an invasive CA, ruling out clinically significant CAD in patients amongst whom the prevalence of disease is low or intermediate [42] and in patients with an equivocal stress test, as recently recommended also by the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology [43]. However, to ensure that this non-invasive test is more accurate, it is important to combine MDCT findings with accurate and complete patient clinical information.

Conflict of Interest None declared

Appendix

The following Investigators and Institutions participated in NIMISCAD (Non Invasive Multicenter Italian Study for Coronary Artery Disease):

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