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CLINICAL RESEARCH
Ischaemic heart disease

Use of cardiac imaging in chronic coronary syndromes: the EURECA Imaging registry

Danilo Neglia [1,2]*†, Riccardo Liga [3,4]†, Alessia Gimelli [1], Tomaž Podlesnikar [5,6], Marta Cvijić[5,7], Gianluca Pontone [8], Marcelo Haertel Miglioranza [9,10,11], Andrea Igoren Guaricci [12], Sara Seitun [13], Alberto Clemente [1], Alexey Sumin [14], João Vitola [15], Antti Saraste [16], Christian Paunonen[16], Ching-Hui Sia [17], Filipp Paleev [18], Leyla Elif Sade [19], Jose Luis Zamorano [20], Natallia Maroz-Vadalazhskaya [21], Constantinos Anagnostopoulos [22], Filipe Macedo [23], Juhani Knuuti [24], Thor Edvardsen [25,26], Bernard Cosyns [27,28], Steffen E. Petersen [29,30], Julien Magne [31,32,33], Cecile Laroche[34], Clara Berlè[34], Bogdan A. Popescu [35], and Victoria Delgado [36,37]*, for the EURECA Investigators‡

[1]Cardiovascular and Imaging Departments, Fondazione Toscana G. Monasterio, Via Giuseppe Moruzzi, 1, 56124 Pisa, Italy; [2]Sant'Anna School of Advanced Studies, Piazza Martiri della Libertà, 33, 56127 Pisa, Italy; [3]Dipartimento di Patologia Chirurgica, Medica, Molecolare e dell' Area Critica, University of Pisa, Via Savi 10, 56126 Pisa, Italy; [4]Dipartimento Cardiotoraco Vascolare, Azienda Ospedaliero-Universitaria Pisana, Via Paradisa, 2, 56124 Pisa, Italy; [5]Department of Cardiology, University Medical Centre Ljubljana, Zaloška cesta 2, 1000 Ljubljana, Slovenia; [6]Department of Cardiac Surgery, University Medical Centre Maribor, Ljubljanska ulica 5, 2000 Maribor, Slovenia; [7]Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000 Ljubljana, Slovenia; [8]Department of Perioperative Cardiology and Cardiovascular Imaging, Centro Cardiologico Monzino IRCCS, Via Carlo Parea, 4, 20138 Milano, Italy; [9]EcoHaertel—Mae de Deus Hospital, R. José de Alencar, 286 - Menino Deus, Porto Alegre - RS, 90880-481, Brazil; [10]Federal University of Health Sciences of Porto Alegre (UFCSPA), R. Sarmento Leite, 245 - Centro Histórico, Porto Alegre - RS, 90050-17, Brazil; [11]Institute of Cardiology—University Foundation of Cardiology, R. Sarmento Leite, 245 - Centro Histórico, Porto Alegre - RS, 90050-170, Brazil; [12]Department of Emergency and Organ Transplantation, Institute of Cardiovascular Disease, University Hospital 'Policlinico' of Bari, Piazza Giulio Cesare, 11, 70124 Bari, Italy; [13]Department of Radiology, IRCCS Policlinico San Martino Hospital, Largo Rosanna Benzi, 10, 16132 Genova, Italy; [14]Federal State Budgetary Scientific Institution "Research Institute for Complex Issues of Cardiovascular Diseases", Sosnoviy Blvd., 6, 650002 Kemerovo, Russian Federation; [15]Quanta Diagnostico por Imagem, R. Alm. Tamandaré, 1000 - Alto da XV, Curitiba - PR, 80045-170, Brazil; [16]Heart Centre, Turku University Hospital and University of Turku, Kiinamyllynkatu 4-8, 20521 Turku, Finland; [17]National University Heart Centre Singapore, 5 Lower Kent Ridge Rd, 119074 Singapore, Singapore; [18]National Medical Research Center of Cardiology, 3-Ya Cherepkovskaya Ulitsa, 15A, 121552 Moscow, Russian Federation; [19]Department of Cardiology, University of Baskent, Yukarı Bahçelievler, Mareşal Fevzi Çakmak Cd. No: 45, 06490 Çankaya/Ankara, Turkey; [20]Department of Cardiology, Ramon Y Cajal University Hospital, M-607, 9, 100, 28034 Madrid, Spain; [21]Department of General Practice, Division of Postgraduate Education, Belarusian State Medical University, Dzerzhinski Ave 83, 220083 Minsk, Belarus; [22]PET-CT Department & Preclinical Imaging Unit, Centre for Experimental Surgery, Clinical and Translational Research, Biomedical Research Foundation Academy of Athens, 4 Soranou Ephessiou Street, 115 27 Athens, Greece; [23]Cardiology Department, S João University Hospital, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal; [24]Turku PET Centre, Turku University Hospital and University of Turku, c/o Turku University Hospital, Kiinamyllynkatu 4-8, 20520 Turku, Finland; [25]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Kirkeveien 166, 0450 Oslo, Norway; [26]Institute of Clinical Medicine, University of Oslo, Klaus Torgårds vei 3, 0372 Oslo, Norway; [27]Centrum voor Hart en Vaatziekten, Universtair Ziekenhuis Brussel, Av. du Laerbeek 101, 1090 Bruxelles, Belgium; [28]In Vivo Molecular and Cellular Imaging Center, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Jette, Belgium; [29]Barts Heart Center, St. Bartholomew's Hospital, West Smithfield, W Smithfield, London EC1A 7BE, UK; [30]NIHR Barts Biomedical Research Centre, William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK; [31]Inserm Unit 1094 and IRD, Faculty of Medicine, Limoges University, 2 rue du Dr Marcland, 87025 Limoges, France; [32]Centre of Epidemiology, Biostatistic and Methodology of Research, University Hospital, Limoges, 2 Av. Martin Luther King, 87000 Limoges, France; [33]Department of Cardiology, Dupuytren-2 University Hospital, 16 rue Bernard Descottes, 87042 Limoges, France; [34]The European Society of Cardiology, The European Heart House, Sophia Antipolis Cedex, 2035 Rte des Colles, 06410 Biot, France; [35]Department of Cardiology, University of Medicine and Pharmacy 'Carol Davila', Euroecolab, Emergency Institute for Cardiovascular Diseases 'Prof. Dr. C. C. Iliescu', Bulevardul Eroii Sanitari 8, 050474 București, Romania; [36]Department of Cardiology, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; and [37]Heart Institute, Hospital University Germans Trias i Pujol, Carretera de Canyet, s/n, 08916, Badalona, Barcelona, Spain

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Abstract

Background The prospective, multicentre EURECA registry assessed the use of imaging and adoption of the European Society of Cardiology (ESC) Guidelines (GL) in patients with chronic coronary syndromes (CCS).

Methods Between May 2019 and March 2020, 5156 patients were recruited in 73 centres from 24 ESC member countries. The adoption of GL recommendations was evaluated according to clinical presentation and pre-test probability (PTP) of obstructive coronary artery disease (CAD).

* Corresponding authors. Tel: +39 0503152019, Fax: +39 0503152166, Cell: +39 3355857594, Email: dneglia@ftgm.it; Tel: +34 934651200, Email: videlga@gmail.com
† Danilo Neglia and Riccardo Liga are joint first co-authors.
‡ The EURECA Investigators are listed in the Appendix.

Results The mean age of the population was 64 ± 11 years, 60% of patients were males, 42% had PTP >15%, 27% had previous CAD, and ejection fraction was <50% in 5%. Exercise ECG was performed in 32% of patients, stress imaging as the first choice in 40%, and computed tomography coronary angiography (CTCA) in 22%. Invasive coronary angiography (ICA) was the first or downstream test in 17% and 11%, respectively. Obstructive CAD was documented in 24% of patients, inducible ischaemia in 19%, and 13% of patients underwent revascularization. In 44% of patients, the overall diagnostic process did not adopt the GL. In these patients, referral to stress imaging (21% vs. 58%; $P < 0.001$) or CTCA (17% vs. 30%; $P < 0.001$) was less frequent, while exercise ECG (43% vs. 22%; $P < 0.001$) and ICA (48% vs. 15%; $P < 0.001$) were more frequently performed. The adoption of GL was associated with fewer ICA, higher proportion of diagnosis of obstructive CAD (60% vs. 39%, $P < 0.001$) and revascularization (54% vs. 37%, $P < 0.001$), higher quality of life, fewer additional testing, and longer times to late revascularization.

Conclusions In patients with CCS, current clinical practice does not adopt GL recommendations on the use of diagnostic tests in a significant proportion of patients. When the diagnostic approach adopts GL recommendations, invasive procedures are less frequently used and the diagnostic yield and therapeutic utility are superior.

Structured Graphical Abstract

Key Question

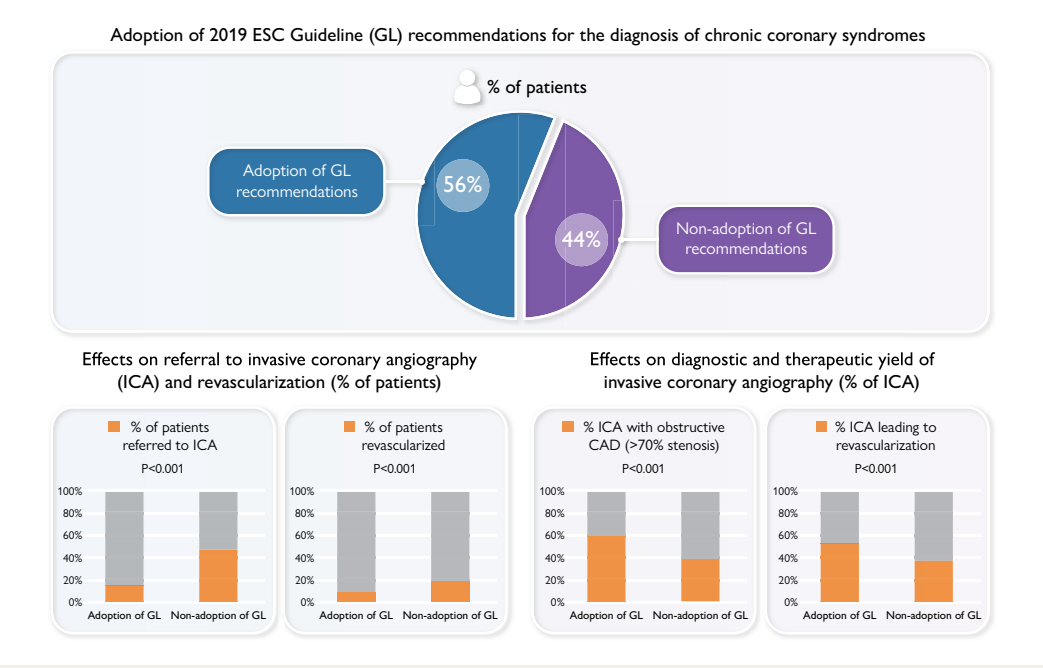
The EURECA registry assessed the rate of adoption of the 2019 European Society of Cardiology (ESC) Guideline (GL) recommendations for the use of non-invasive and invasive imaging tests in a contemporary large population of 5,156 patients with known or suspected chronic coronary syndrome (CCS) enrolled in ESC member or affiliated countries.

Key Finding

A lower proportion of invasive coronary angiographies (ICA) (15% vs 48%) and of revascularizations (8% vs 19%) were performed in the 56% of patients in whom GL recommendations were adopted as compared to the remaining 44%. In patients managed according to GL, ICA more frequently documented obstructive coronary artery disease (CAD) (60% vs 39%) leading to revascularization (54% vs 37%).

Take Home Message

In a contemporary population of patients with known or suspected CCS, the prevalence of obstructive CAD and of significant ischaemia is relatively low. The use of imaging tests following the 2019 ESC GL recommendations results in a reduction of invasive procedures, improved diagnostic yield, and better identification of candidates for coronary revascularization.



In the whole population of patients with chronic coronary syndromes (CCS) enrolled in the EURECA registry, 56% of patients were managed according to the 2019 European Society of Cardiology (ESC) Guidelines (GL) for the overall diagnostic process. The adoption of GL recommendations led to a lower proportion of invasive coronary angiograms (15% vs. 48%) and coronary revascularizations (8% vs. 19%). However, when invasive angiograms were performed adopting GL recommendations, 60% showed obstructive coronary artery disease (CAD) (>70% stenosis) and 54% led to revascularization as compared with 39% and 37%, respectively, when the diagnostic process did not adopt the GL recommendations.

Keywords Coronary artery disease • Chronic coronary syndromes • Imaging

Introduction

In the last decades, the prevalence and associated mortality of cardiovascular disease have been globally declining in Europe, but this trend is not homogeneous in all countries[1] possibly mirroring the regional variability in risk factors and health expenditures.[2] Ischaemic heart disease still represents a major cause of death in European countries[1] and a relevant determinant of healthcare costs. In patients with chronic coronary syndromes (CCS), the increasing and variable use of cardiovascular imaging and of invasive procedures in the European Society of Cardiology (ESC) member countries[3,4] has underlined the need for standardization[5,6] and has raised concerns on potential inequalities in availability and accessibility of resources across countries.[7]

The 2019 ESC guidelines (GL) for the management of CCS[8,9] provided a scientifically updated framework for a more uniform, appropriate and effective utilization of imaging in the diagnostic process of coronary artery disease (CAD). In particular, due to the decreased prevalence of obstructive CAD and significant myocardial ischaemia,[9–11] the GL used updated models for the estimation of the pre-test probability (PTP) of obstructive CAD[12,13] to guide the use of cardiac imaging and more specifically to identify high-risk patients that would deserve invasive management strategies. Specific indications for non-invasive and/or invasive imaging have been identified for different clinical scenarios, particularly relevant in symptomatic patients with or without left ventricular dysfunction or previous CAD. Based on the best possible evidence,[14–16] GL recommendations are aimed at reducing the inappropriate use of technologies and potential risks for patients while improving outcomes. One of the key factors conditioning effectiveness of GL is the degree of their adoption in routine clinical practice, which in turn is influenced by the variability of healthcare systems in different countries, costs, test availability, local expertise, and preferences.

The EURECA registry was designed as a prospective international multicentre registry to assess the adoption of the 2019 ESC GL recommendations for the use of non-invasive and invasive imaging tests in a contemporary large population of patients with CCS enrolled in ESC member or affiliated countries.

Materials and methods

Data collection

Symptomatic patients with known (history of previous CAD) or suspected CCS, referred to cardiology outpatient clinics or other laboratories for diagnostic evaluation, were enrolled consecutively between May 2019 and March 2020 in 73 centres from 24 ESC member or affiliated countries. Participating countries were grouped in five European and non-European regions as follows: (i) Northern Europe—Finland, Lithuania, Norway, Sweden; (ii) Western Europe—Austria, Belgium, France, Netherlands, Switzerland; (iii) Eastern Europe—Belarus, Hungary, Poland, Romania, Russian Federation; (iv) Southern Europe—Greece, Italy, Portugal, Serbia, Slovenia, Spain, Turkey; and (v) non-European—Brazil, Egypt, Singapore.

The inclusion criteria, aiming at enrolling only patients with CCS avoiding those with unstable conditions, were the presence of stable chest pain (typical, atypical, or non-anginal), dyspnoea or fatigue on exertion, with suspected or known CAD, requiring further evaluation.

The main exclusion criteria were: (i) recent (<6 months) hospitalization for CAD or heart failure with or without coronary revascularization; (ii) chest pain in the context of an acute coronary syndrome; (iii) severe symptoms such as unstable angina and typical angina at a very low level of exercise (or equivalents); (iv) other severe cardiac conditions [significant (moderate and severe) valvular heart disease, sustained ventricular arrhythmias, sick sinus syndrome or high degree atrioventricular block, complex congenital heart disease, acute heart failure]; (v) significant comorbidities limiting survival (cancer, chronic debilitating conditions); (vi) inability to provide informed consent; and (vii) being enrolled or planned to be enrolled in a pharmacological interventional clinical trial. The study was performed according to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki. Local and/or national Ethics Committees or Institutional Review Boards approved the registry protocol according to local regulations. All patients signed a written informed consent to participate in the registry in conjunction with local investigators. A central registry-specific database was created by collecting pseudonymized data at the European Heart House in France.

Standard management of patients was performed as per routine clinical practice, including drug prescriptions and indications to perform diagnostic/therapeutic procedures.

Clinical data and quality of life (QoL) information (EQ-5D-5L questionnaire) were collected in all patients. The Visual Analog Scale (VAS) self-reported score and the Index Score (using cTTO model) were used as synthetic QoL variables. A pre-test probability of obstructive CAD was estimated for each patient based on age, sex, and type of symptoms according to the updated predictive model included in the 2019 ESC GL.[9,13]

Baseline clinical data, QoL information, diagnostic procedures, test results, final diagnosis reached after all tests, and early clinical management decisions (including revascularization procedures and change in medical treatment) were collected and registered in the 6 months after enrolment. After the completion of the diagnostic work-up and of early clinical management, 6-month follow-up data were obtained for each participant by outpatient visit or telephone interview, including QoL information, symptoms, additional tests performed, and clinical events.

Imaging protocols

Standard acquisition and interpretation protocols, shared among all centres before the initiation of the registry, were used for each diagnostic test. The definition of high-risk positive results for each stress imaging test and computed tomography coronary angiography (CTCA) are detailed in Supplementary material online, *Figure S1*.[9,17]

Study endpoint

The primary endpoint was the adoption of the 2019 ESC GL recommendations in the use of non-invasive and invasive imaging strategies for the management of patients with known or suspected CCS.[9] The criteria used to define adoption are graphically summarized in *Figure 1*. Based on the estimated PTP of obstructive CAD, the absence/presence of known CAD and of left ventricular ejection fraction (LVEF) < 50% six scenarios were identified and for each scenario, adoption was defined for the choice of the first non-invasive or invasive imaging test (endpoint a) and for the overall diagnostic process (endpoint b), including both the result of the first imaging test and the use of additional testing. The adoption of GL recommendations to diagnose CAD was defined in each clinical scenario as follows:

- Scenario 1: No test performed in patients with suspected CAD and PTP ≤5%;
- Scenario 2: In patients with suspected CAD and 5%<PTP ≤ 15%, non-invasive imaging test (CTCA or stress imaging) performed as first test and, if the results of the first test were inconclusive or non-

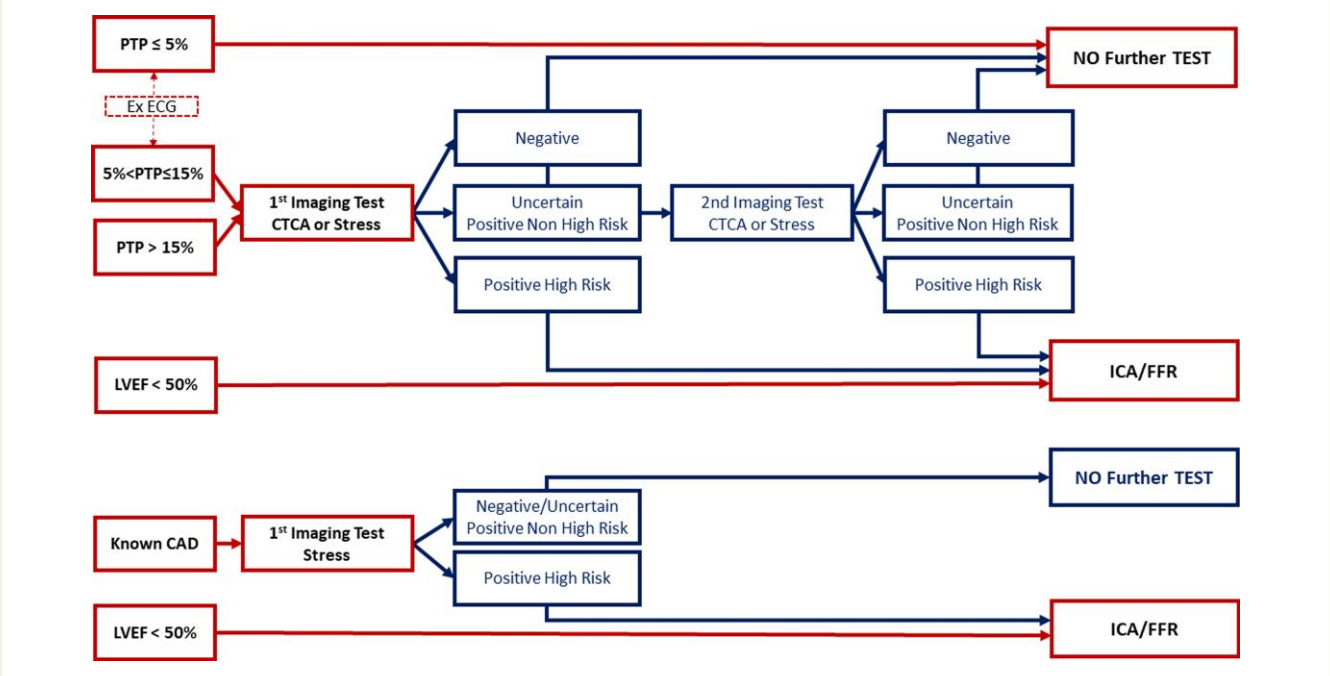


Figure 1 Definition of adoption of 2019 ESC GL recommendations for the use of imaging in patients without known CAD (upper panel) or with known CAD (lower panel). Criteria to define adoption of GL recommendations in the choice of the first non-invasive or invasive imaging test are identified in the flowchart by red lines. Additional criteria to define the adoption of GL recommendations in the choice of further imaging tests are identified in the flowchart by blue lines. In patients without known CAD and PTP ≤5% or 5%<PTP ≤ 15%, exercise ECG (when performed) was considered as potential modifier of clinical likelihood (dotted lines). Details on the criteria used in each scenario are fully reported in the methods section. CTCA, computed tomography coronary angiography; FFR, fractional flow reserve; ICA, invasive coronary angiography; PTP, pre-test probability of obstructive CAD.

high risk, a second non-invasive imaging test performed leading to no further test (in case of negative, inconclusive or non-high risk results of the second test) or to invasive coronary angiography (ICA) (in case of positive high risk results of the second test);

- Scenario 3: In patients with suspected CAD and PTP >15%, non-invasive imaging test (CTCA or stress imaging) performed as first test and, if the results of the first test were inconclusive or non-high risk, a second non-invasive imaging test performed leading to no further test (in case of negative, inconclusive or non-high risk results of the second test) or to ICA (in case of positive high risk results of the second test);
- Scenario 4: In patients with suspected CAD and LVEF <50%, ICA performed as first test;
- Scenario 5: In patients with known CAD and LVEF >50%, non-invasive stress imaging performed as first test, followed by ICA in case of positive high risk results;
- Scenario 6: In patients with known CAD and LVEF <50%, ICA performed as first test.

Furthermore, in patients with suspected CAD and PTP ≤5% or with 5%<PTP ≤ 15%, exercise ECG results (when performed) were also considered as potential modifiers of the clinical likelihood; therefore, the adoption of GL recommendations also included performing non-invasive imaging tests in those patients with PTP ≤5% and a positive exercise ECG as well as not performing any other test in those patients with 5%<PTP ≤ 15% and a negative exercise ECG.

Statistical analyses

Continuous variables were reported as mean ± standard deviation or as median and interquartile range (IQR). Among-group comparisons were performed using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as counts and percentages. Among-group comparisons were performed using a χ^2 test or the Fisher's exact test (if any expected cell count was less than five). For qualitative variables, with more than two possibilities, the Monte Carlo estimates of the exact *P*-values were used.

A backward multiple logistic regression analysis was used to determine the factors associated with the adoption of ESC GL recommendations, including in the models all relevant variables with $P < 0.05$ in univariable analysis. Logistic regression analysis for 'endpoint a' included variables related with characteristics of the enrolling centres, demographic and clinical characteristics of the patients, including performance of exercise ECG, as possible determinants in the choice of the first imaging test. Logistic regression analysis for 'endpoint b' also included variables indicating the use of non-invasive imaging and invasive imaging tests (independently whether as first test and independently of test results) in the overall diagnostic process. Specifically, different stress imaging modalities were aggregated into a variable defined as 'integrated stress imaging'. Sensitivity analyses in patients without previous CAD and in patients who completed the overall baseline management (up to final diagnosis and early treatment) before or after the COVID-19 pandemic outbreak in February 2020 were performed by the same statistical means. A significance level

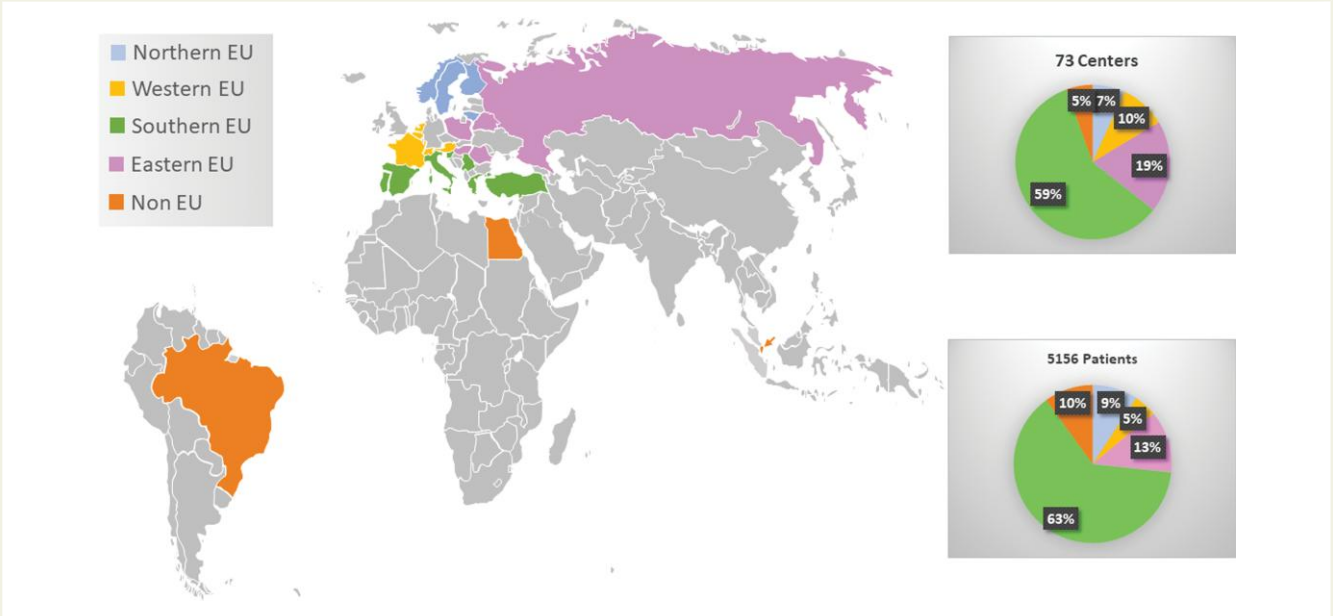


Figure 2 Countries participating in the EURECA registry are indicated on the world map and coloured according to the attributed geographical region. EU, European ESC member/affiliated countries; non-EU, non-European ESC member/affiliated countries (Brazil, Singapore) and North Africa (Egypt). The percentage distribution of enrolling centres and of enrolled patients per geographical region is reported. Southern Europe includes 59% of centres and 63% of the whole population. Eastern/Northern/Western Europe together account for 36% of centres and 27% of the whole population, while non-European regions account for 5% of centres and 10% of the population.

of 0.05 was required for a variable to stay in the model. No interaction was tested. A Hosmer and Lemeshow goodness-of-fit test was used to verify that the model was optimal. A two-sided *P*-value <0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Study population

A total of 5156 patients were enrolled in 73 centres from 24 countries. The geographical distribution of the EURECA population and of the recruiting centres are summarized in *Figure 2*. Overall, 74% of patients were enrolled at university centres and 72% in cardiology or cardiovascular departments. The availability of exercise ECG was reported in 99% of centres, of at least one or two non-invasive stress imaging modalities in 100% and 81%, respectively, of CTCA in 93%, of ICA in 94%, and of invasive measurement of fractional flow reserve/instantaneous wave-free ratio (FFR/iFR) in 85%.

The mean age of the population was 64 ± 11 years and 60% of patients were men. Typical angina was reported by 26% of patients, atypical angina (or chest pain equivalents) by 56%, and non-anginal chest pain by 18%. Only 5% of patients had a PTP of obstructive CAD ≤5%, while 42% had a PTP >15%. Previous CAD was known in 27%, of which 87% had been revascularized. LVEF was <50% in 5% of patients (2% without and 3% with known CAD). The baseline characteristics of the entire population and of patient subgroups, based on the absence or presence of previous CAD, values of PTP and of LVEF, are summarized in *Table 1*. In the overall population, hypertension (69%) and dyslipidaemia (64%) were the most prevalent risk factors. The prevalence of major risk factors progressively increased according to PTP values and was highest among patients with LVEF <50% and/or with previous CAD.

Final clinical diagnosis and early management

Investigators reported the presence of obstructive CAD as the final diagnosis in 24% of patients and of inducible ischaemia in 19% of patients. The relative prevalence of obstructive, non-obstructive CAD, inducible ischaemia, and the early management decisions in the overall population and across subgroups are depicted in *Figure 3*. The final diagnosis of obstructive CAD and of inducible ischaemia, posed after all tests, was in line with the predicted prevalence based on increasing PTP values, LVEF, and previous CAD. On the other hand, non-obstructive CAD was diagnosed in 38% of the entire population, without differences across subgroups. Early management included coronary revascularization in 13% of patients (percutaneous coronary intervention in 11% and coronary artery bypass grafting in 2%) and a change in medical treatment (with or without the addition of new drugs) in 38% of patients. Either revascularization procedures or a change in medical treatment were progressively more frequent across subgroups as the prevalence of obstructive CAD and ischaemia.

Use of imaging tests in subgroups and test results

The use and results of exercise ECG, CTCA, stress imaging, and ICA performed in the overall population and in different patient subgroups are reported in *Table 2*. Exercise ECG was performed in 32% of patients, with the highest use in patients with PTP ≤5% (50%), progressively decreasing in groups with higher PTP, LVEF <50%, and/or

Table 1 Clinical characteristics of the study population

Variables	Whole population	Patients without previous CAD					Patients with previous CAD		
	N = 5156 (100%)	PTP ≤5% *N* = 273 (5.3%)	5%<PTP ≤15% *N* = 1244 (24.1%)	PTP >15% *N* = 2171 (42.1%)	LVEF <50% *N* = 98 (1.9%)	*P*-value	LVEF ≥50% *N* = 1209 (23.4%)	LVEF <50% *N* = 161 (3.1%)	*P*-value
Demographic data									
Age (years) Missing = 0	63.5 (±11.3)	42.4 (±9.3)	57.8 (±9.2)	67.3 (±9.1)	68.4 (±11.5)	<0.001	66.4 (±9.6)	66.7 (±9.6)	0.912
Female sex Missing = 0	2076 (40.3%)	146 (53.5%)	1001 (80.5%)	624 (28.7%)	29 (29.6%)	<0.001	252 (20.8%)	24 (14.9%)	0.078
BMI (kg/m^2) Missing = 513	27.9 (±4.8)	26.9 (±5.1)	27.9 (±5.2)	27.9 (±4.6)	28.1 (±4.8)	0.007	28.1 (±4.5)	28.2 (±4.5)	0.920
Symptoms									
Typical angina Missing = 1	1359/5155 (26.4%)	15/273 (5.5%)	126/1244 (10.1%)	749/2170 (34.5%)	15/98 (15.3%)	<0.001	390/1209 (32.3%)	64/161 (39.8%)	0.065
Atypical angina (or chest pain equivalents)	2881/5155 (55.9%)	82/273 (30.0%)	824/1244 (66.2%)	1191/2170 (54.9%)	61/98 (62.2%)		641/1209 (53.0%)	82/161 (50.9%)	
Non-anginal chest pain	915/5155 (17.7%)	176/273 (64.5%)	294/1244 (23.6%)	230/2170 (10.6%)	22/98 (22.4%)		178/1209 (14.7%)	15/161 (9.3%)	
Cardiovascular risk factors									
Family history Missing = 619	1724/4537 (38.0%)	93/243 (38.3%)	462/1111 (41.6%)	661/1900 (34.8%)	28/82 (34.1%)	0.003	433/1062 (40.8%)	47/139 (33.8%)	0.115
Smoking Missing = 165	2155/4991 (43.2%)	96/268 (35.8%)	389/1194 (32.6%)	878/2093 (41.9%)	52/97 (53.6%)	<0.001	641/1183 (54.2%)	99/156 (63.5%)	0.028
Diabetes mellitus Missing = 37	1125/5119 (22.0%)	18/272 (6.6%)	224/1236 (18.1%)	475/2156 (22.0%)	19/96 (19.8%)	<0.001	333/1199 (27.8%)	56/160 (35.0%)	0.057
Dyslipidemia Missing = 149	3220/5007 (64.3%)	77/262 (29.4%)	654/1196 (54.7%)	1315/2101 (62.6%)	57/97 (58.8%)	<0.001	981/1191 (82.4%)	136/160 (85.0%)	0.409
Hypertension Missing = 51	3541/5105 (69.4%)	87/272 (32.0%)	711/1231 (57.8%)	1559/2145 (72.7%)	75/97 (77.3%)	<0.001	978/1199 (81.6%)	131/161 (81.4%)	0.951
Obesity Missing = 145	1394/5011 (27.8%)	55/264 (20.8%)	322/1191 (27.0%)	592/2111 (28.0%)	28/97 (28.9%)	0.097	349/1190 (29.3%)	48/158 (30.4%)	0.785
Previous CAD history									
Old MI Missing = 90	892/5066 (17.6%)	0/269 (0.0%)	0/1232 (0.0%)	0/2140 (0.0%)	0/91 (0.0%)	NA	750/1180 (63.6%)	142/154 (92.2%)	<0.001
Previous revascularization Missing = 7	1197/5149 (23.2%)	0/273 (0.0%)	0/1242 (0.0%)	0/2168 (0.0%)	0/98 (0.0%)	NA	1063/1207(88.1%)	134/161 (83.2%)	0.081

Continued

Table 1 *Continued*

Variables	Whole population	Patients without previous CAD					Patients with previous CAD		
	N = 5156 (100%)	PTP ≤5% *N* = 273 (5.3%)	5%<PTP ≤15% *N* = 1244 (24.1%)	PTP >15% *N* = 2171 (42.1%)	LVEF <50% *N* = 98 (1.9%)	*P*-value	LVEF ≥50% *N* = 1209 (23.4%)	LVEF <50% *N* = 161 (3.1%)	*P*-value
Previous PCI Missing = 7	1042/5149 (20.2%)	0/273 (0.0%)	0/1242 (0.0%)	0/2168 (0.0%)	0/98 (0.0%)	NA	933/1207 (77.3%)	109/161 (67.7%)	0.007
Previous CABG Missing = 7	257/5149 (5.0%)	0/273 (0.0%)	0/1242 (0.0%)	0/2168 (0.0%)	0/98 (0.0%)	NA	209/1207 (17.3%)	48/161 (29.8%)	<0.001
LV function									
Measured LVEF (%) Missing = 2361	58.1 (±8.0)	62.7 (±5.5)	61.3 (±5.2)	60.2 (±5.2)	40.8 (±5.7)	<0.001	58.4 (±5.7)	40.7 (±6.3)	<0.001

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTP, pre-test probability.

previous CAD. In 20% of patients, no imaging test (either non-invasive or invasive) was performed, with a similar trend across subgroups (*Figure 4*). Among non-invasive imaging tests, CTCA was performed in 24% of patients, more frequently in patients with normal left ventricular function and without previous CAD, independently of PTP estimation. Stress imaging was performed in 41% of patients, mainly by SPECT or echocardiography (23% and 16%) and its use increased progressively from lower PTP to higher PTP groups, LVEF <50% and/or previous CAD. Non-invasive imaging modalities were rarely used as additional tests after another imaging exam. ICA was performed in 29% of patients and in a substantial proportion (17%) as the first imaging test. It was used in all subgroups and its use increased progressively from lower PTP to higher PTP, LVEF <50%, and/or previous CAD (*Figure 4*). FFR or iFR measurements during ICA were done in a minority of cases (7% of patients).

The proportion of patients with high-risk results, documented by each single non-invasive stress imaging modality, ranged between 0.1% and 6% of the population. It was 9% by all stress imaging modalities combined and 3% by CTCA. The proportion of patients with obstructive CAD (>70% stenosis) at ICA was 13% of the population and the proportion of patients with abnormal FFR/iFR was 0.6%. The prevalence of positive high-risk results of non-invasive imaging tests and of obstructive CAD at ICA differed across different subgroups generally increasing from patients with lower to those with higher PTP, LVEF <50%, or previous CAD (*Table 2*). The number of patients undergoing exercise ECG, non-invasive imaging tests and ICA, together with the number of non-invasive exams with abnormal or high-risk results and of ICA showing obstructive CAD (>70% stenosis), are shown in *Figure 5*. The choice of further testing after the results of the first test in the different patient subgroups is summarized in Supplementary material online, *Figures S2 and S3*.

Adoption of ESC guideline recommendations and effects on initial patient management

The adoption of ESC GL recommendations could not be defined in 150/5156 patients for 'endpoint a' (3%) and in 161/5156 patients for 'endpoint b' (3%) mainly due to scheduled tests not performed for unspecified reasons. The diagnostic process adopted the ESC GL recommendations in the choice of the first imaging test in 3144 patients (63%) and for the overall diagnostic process in 2783 patients (56%). The proportion of patients managed according to the GL recommendations in the different patient subgroups tended to decrease along with increasing PTP of obstructive CAD or known CAD, with the exception of patients with PTP ≤5% in whom the adoption of GL recommendations was lower than the average (see Supplementary material online, *Figure S4*). The univariable and multivariable analyses for predictors of adoption of GL recommendations for the overall diagnostic process (endpoint b) are reported in *Table 3*. At univariable analysis, patients managed according to the GL recommendations (vs. non-adoption of GL recommendations) were less frequently enrolled in cardiology/cardiovascular departments and university centres, were younger and more frequently females, had a lower cardiovascular risk profile, a lower prevalence of typical angina, a lower rate of known CAD (previous myocardial infarction and/or coronary revascularization), and underwent less frequently exercise ECG. Patients managed according to the GL recommendations (vs. non-adoption of GL recommendations) were more frequently referred to stress imaging (58% vs. 21%; *P* <

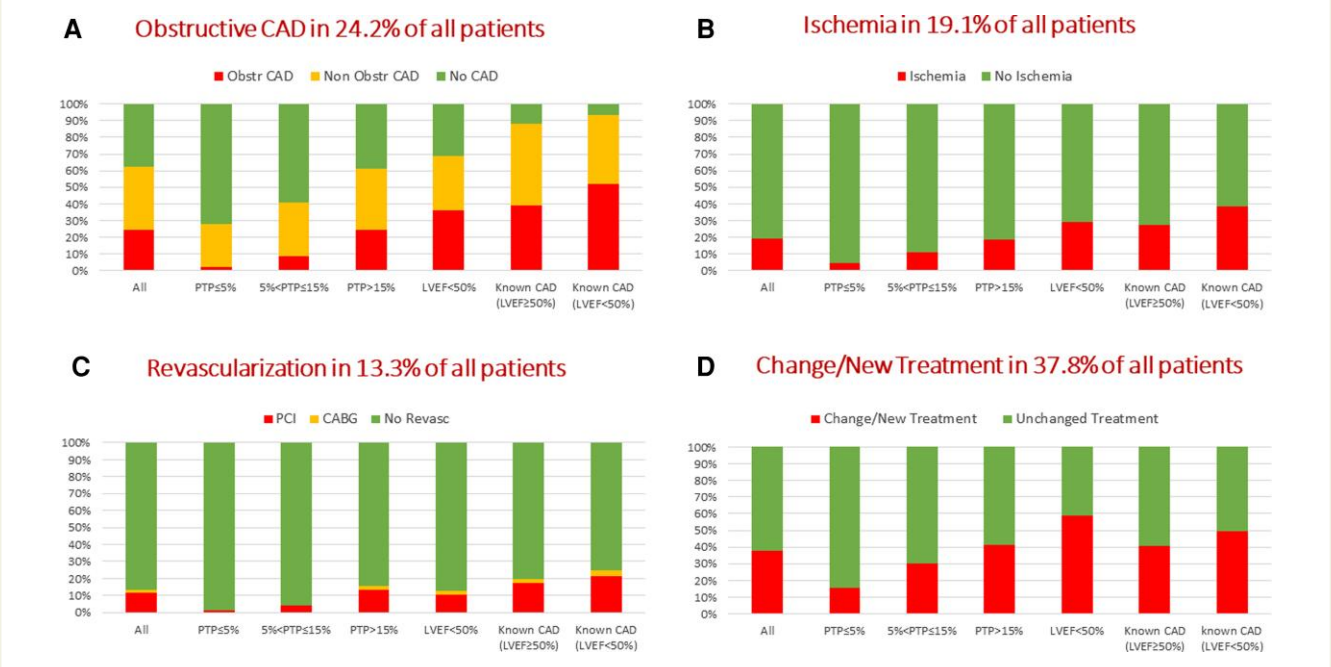


Figure 3 The final diagnosis of obstructive/non-obstructive/absent CAD (*Panel A*), of inducible ischaemia (*Panel B*), as well as the early decision of revascularization (*Panel C*) and/or change in medical treatment (*Panel D*) are summarized as a percentage of patients of the whole population and of subgroups with or without known CAD, further defined by increasing PTP values and LVEF.

0.001) or CTCA (30% vs. 17%; $P < 0.001$), and less frequently to ICA (15% vs. 48%; $P < 0.001$). At multivariable analysis, male sex, older age, family history of CAD, dyslipidemia, previous coronary revascularization, performing exercise ECG, and referral to ICA were associated with a lower likelihood of adoption of GL recommendations, while referral to stress imaging and CTCA were independently associated with a higher likelihood of adoption of GL recommendations (*Table 3*).

In patients managed according to the GL recommendations (vs. non-adoption of GL recommendations), invasive diagnostic and therapeutic procedures were less frequently performed (ICA 15% vs. 48% and coronary revascularizations 8% vs. 19%, $P < 0.001$). However, the diagnostic yield of ICA was higher, and a higher proportion of ICA led to coronary revascularization. For every 100 ICA performed according to the GL recommendations, obstructive CAD (>70% stenosis) was documented in 60% and revascularization performed in 54% as compared with 39% and 37%, when ICA was performed not adopting to GL recommendations ($P < 0.001$) (*Structured Graphical Abstract*). On the other hand, adoption of GL recommendations was associated with a less frequent change in medical treatments and/or addition of new drugs (30% vs. 45%, $P < 0.001$).

The univariable and multivariable analysis for predictors of adoption of GL recommendations in the choice of the first test (endpoint a) are reported in Supplementary material online, *Table S1* showing similar results as for the overall diagnostic process.

The results of sensitivity analysis in patients without previous CAD (Supplementary material online, *Table S2*) showed fewer independent clinical determinants of non-adoption (male sex, dyslipidemia), the same imaging determinants of adoption (stress imaging and CTCA) and of non-adoption (referral to ICA) as compared with the analysis in the whole population. Performing exercise ECG was still associated with non-adoption of GL recommendations at univariable analysis but was no more an independent determinant at multivariable analysis.

In patients who completed the whole baseline management after the COVID-19 pandemic outbreak (22%), exercise ECG was performed in the same proportion as in patients managed before the outbreak (32% vs. 32%, ns) with less frequent positive results (15% vs. 25%, $P < 0.001$), stress imaging and CTCA were performed less frequently (38% vs. 42%, $P = 0.02$ and 14% vs. 27%, $P < 0.001$) with less frequent positive CTCA results (2% vs. 4%, $P < 0.01$). On the other hand, ICA was used more frequently as first test (20% vs. 17%, $P = 0.01$) with non-significantly lower positive high risk results (12% vs. 14%, $P > 0.05$) (Supplementary material online, *Table S3*). The results of the sensitivity analyses performed in patients managed after the outbreak showed that male sex, previous revascularization, and referral to ICA remained independently associated with a lower likelihood of adoption of GL recommendations while referral to stress imaging and CTCA remained independently associated with a higher likelihood of adoption of GL recommendations. On the other hand, typical angina and hypertension were additional determinants of non-adoption of GL recommendations while performing exercise ECG was no more an independent determinant of non-adoption of GL recommendations. Sensitivity analyses in patients managed before and after the COVID-19 pandemic outbreak are reported in Supplementary material online, *Tables S4 and S5*.

Adoption of ESC guideline recommendations and follow-up

Patients were followed for a median of 172 days (interquartile range 74 days). Of the 4995 patients in whom adoption or non-adoption of GL recommendations for the overall diagnostic process could be

Table 2 Use and results of exercise ECG and imaging tests in different patient categories

Variables	Whole population	Patients without previous CAD					Patients with previous CAD		
	N = 5156 (100%)	PTP ≤5% *N* = 273 (5.3%)	5%<PTP ≤ 15% *N* = 1244 (24.1%)	PTP >15% *N* = 2171 (42.1%)	LVEF <50% *N* = 98 (1.9%)	*P*-value	LVEF ≥50% *N* = 1209 (23.4%)	LVEF <50% *N* = 161 (3.1%)	*P*-value
Exercise ECG									
Performed	1651/5156 (32%)	137/273 (50.2%)	448/1244 (36.0%)	655/2171 (30.2%)	20/98 (20.4%)	<0.001	372/1209 (30.8%)	19/161 (11.8%)	<0.001
Positive	383/5156 (7.4%)	15/273 (5.5%)	82/1244 (6.6%)	175/2171 (8.1%)	4/98 (4.1%)	0.133	101/1209 (8.4%)	6/161 (3.7%)	0.040
Stress ECHO									
Performed	803/5156 (15.6%)	29/273 (10.6%)	163/1244 (13.1%)	318/2171 (14.6%)	9/98 (9.2%)	0.117	236/1209 (19.5%)	48/161 (29.8%)	0.002
First test	783/5156 (15.2%)	29/273 (10.6%)	162/1244 (13.0%)	308/2171 (14.2%)	8/98 (8.2%)	0.142	229/1209 (18.9%)	47/161 (29.2%)	0.002
Positive HR	115/5156 (2.2%)	0/273 (0.0%)	7/1244 (0.6%)	48/2171 (2.2%)	4/98 (4.1%)	<0.001	42/1209 (3.5%)	14/161 (8.7%)	0.002
Stress CMR									
Performed	76/5156 (1.5%)	0/273 (0.0%)	7/1244 (0.6%)	20/2171 (0.9%)	1/98 (1.0%)	0.245	42/1209 (3.5%)	6/161 (3.7%)	0.870
First test	68/5156 (1.3%)	0/273 (0.0%)	6/1244 (0.5%)	18/2171 (0.8%)	1/98 (1.0%)	0.259	37/1209 (3.1%)	6/161 (3.7%)	0.649
Positive HR	14/5156 (0.3%)	0/273 (0.0%)	0/1244 (0.0%)	4/2171 (0.2%)	0/98 (0.0%)	0.538	6/1209 (0.5%)	4/161 (2.5%)	0.022
Stress SPECT									
Performed	1202/5156 (23.3%)	37/273 (13.6%)	264/1244 (21.2%)	526/2171 (24.2%)	34/98 (34.7%)	<0.001	290/1209 (24.0%)	51/161 (31.7%)	0.034
First test	1166/5156 (22.6%)	36/273 (13.2%)	258/1244 (20.7%)	507/2171 (23.4%)	34/98 (34.7%)	<0.001	280/1209 (23.2%)	51/161 (31.7%)	0.018
Positive HR	310/5156 (6.0%)	3/273 (1.1%)	36/1244 (2.9%)	123/2171 (5.7%)	12/98 (12.2%)	<0.001	114/1209 (9.4%)	22/161 (13.7%)	0.091
Stress PET									
Performed	21/5156 (0.4%)	2/273 (0.7%)	5/1244 (0.4%)	11/2171 (0.5%)	1/98 (1.0%)	0.495	1/1209 (0.1%)	1/161 (0.6%)	0.221
First test	17/5156 (0.3%)	1/273 (0.4%)	2/1244 (0.2%)	11/2171 (0.5%)	1/98 (1.0%)	0.186	1/1209 (0.1%)	1/161 (0.6%)	0.221
Positive HR	3/5156 (0.1%)	0/273 (0.0%)	0/1244 (0.0%)	1/2171 (0.0%)	0/98 (0.0%)	>0.999	1/1209 (0.1%)	1/161 (0.6%)	0.221
Stress CT perfusion									
Performed	37/5156 (0.7%)	0/273 (0.0%)	7/1244 (0.6%)	11/2171 (0.5%)	1/98 (1.0%)	0.481	18/1209 (1.5%)	0/161 (0.0%)	0.256
First test	37/5156 (0.7%)	0/273 (0.0%)	7/1244 (0.6%)	11/2171 (0.5%)	1/98 (1.0%)	0.481	18/1209 (1.5%)	0/161 (0.0%)	0.256
Positive HR	12/5156 (0.2%)	0/273 (0.0%)	2/1244 (0.2%)	3/2171 (0.1%)	1/98 (1.0%)	0.265	6/1209 (0.5%)	0/161 (0.0%)	>0.999
Integrated stress imaging									
Performed	2127/5156 (41.3%)	68/273 (24.9%)	446/1244 (35.9%)	882/2171 (40.6%)	46/98 (46.9%)	<0.001	579/1209 (47.9%)	106/161 (65.8%)	<0.001
First test	2070/5156 (40.1%)	66/273 (24.2%)	435/1244 (35.0%)	855/2171 (39.4%)	45/98 (45.9%)	<0.001	564/1209 (46.7%)	105/161 (65.2%)	<0.001
Positive HR	454/5156 (8.8%)	3/273 (1.1%)	45/1244 (3.6%)	179/2171 (8.2%)	17/98 (17.3%)	<0.001	169/1209 (14.0%)	41/161 (25.5%)	<0.001

Continued

Table 2 *Continued*

Variables	Whole population	Patients without previous CAD					Patients with previous CAD		
	N = 5156 (100%)	PTP ≤5% *N* = 273 (5.3%)	5%<PTP ≤ 15% *N* = 1244 (24.1%)	PTP >15% *N* = 2171 (42.1%)	LVEF <50% *N* = 98 (1.9%)	*P*-value	LVEF ≥50% *N* = 1209 (23.4%)	LVEF <50% *N* = 161 (3.1%)	*P*-value
CT coronary angiography									
Performed	1219/5156 (23.6%)	65/273 (23.8%)	362/1244 (29.1%)	587/2171 (27.0%)	19/98 (19.4%)	0.076	178/1209 (14.7%)	8/161 (5.0%)	0.001
First test	1157/5156 (22.4%)	64/273 (23.4%)	346/1244 (27.8%)	555/2171 (25.6%)	18/98 (18.4%)	0.101	168/1209 (13.9%)	6/161 (3.7%)	<0.001
Positive HR	177/5156 (3.4%)	0/273 (0.0%)	14/1244 (1.1%)	97/2171 (4.5%)	2/98 (2.0%)	<0.001	62/1209 (5.1%)	2/161 (1.2%)	0.028
Invasive coronary angiography									
Performed	1486/5156 (28.8%)	21/273 (7.7%)	229/1244 (18.4%)	682/2171 (31.4%)	48/98 (49.0%)	<0.001	433/1209 (35.8%)	73/161 (45.3%)	0.019
First test	897/5156 (17.4%)	15/273 (5.5%)	136/1244 (10.9%)	401/2171 (18.5%)	32/98 (32.7%)	<0.001	274/1209 (22.7%)	39/161 (24.2%)	0.658
Positive HR	664/5156 (12.9%)	4/273 (1.5%)	51/1244 (4.1%)	302/2171 (13.9%)	15/98 (15.3%)	<0.001	247/1209 (20.4%)	45/161 (28.0%)	0.029
FFR measured	91/1486 (6.1%)	3/21 (14.3%)	12/229 (5.2%)	39/682 (5.7%)	3/48 (6.3%)	0.342	30/433 (6.9%)	4/73 (5.5%)	0.803
FFR abnormal	23/91 (25.3%)	1/3 (33.3%)	1/12 (8.3%)	12/39 (30.8%)	1/3 (33.3%)	0.405	7/30 (23.3%)	1/4 (25.0%)	>0.999
iFR measured	20/1486 (1.3%)	1/21 (4.8%)	2/229 (0.9%)	6/682 (0.9%)	0/48 (0.0%)	0.302	10/433 (2.3%)	1/73 (1.4%)	>0.999
iFR abnormal	8/20 (40.0%)	0/1 (0.0%)	0/2 (0.0%)	2/6 (33.3%)	–	>0.999	5/10 (50%)	1/1 (100.0%)	>0.999

Integrated stress imaging: integrated variable expressing whether one non-invasive stress imaging test (any modality) was performed, whether first and whether with high risk results; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CT, computed tomography; HR, high risk; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LVEF, left ventricular ejection fraction; PET, positron emission tomography; PTP, pre-test probability; SPECT, single photon emission computed tomography.

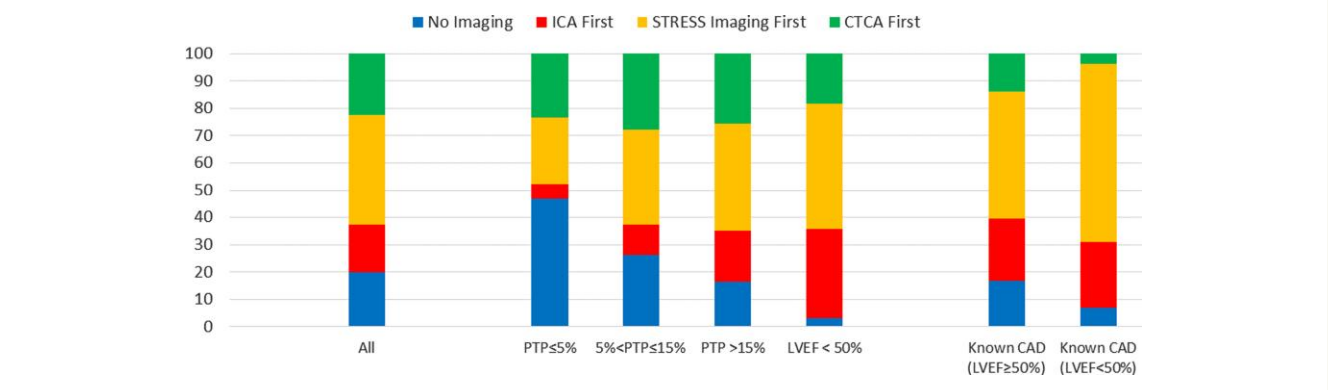


Figure 4 The percentages of patients who did not perform any imaging test (exercise ECG only) and of patients who underwent invasive coronary angiography (ICA), a stress imaging modality or computed tomography coronary angiography (CTCA) as a first test in the whole population and for each subgroup is represented. See text for description.

Figure 5 The number of patients undergoing exercise ECG, non-invasive imaging or invasive exams is reported in the bar graph. Red bars indicate the number of patients with an abnormal test (for exercise ECG and for FFR/iFR), high risk test results (for non-invasive imaging modalities) or obstructive CAD (>70% stenosis) (for ICA). See Supplementary material online, *Figure S1* for definitions. Others, PET or CT perfusion studies.

defined, 4262 (85%) completed the follow-up. Major adverse cardiovascular events (MACE), including cardiac death or non-fatal myocardial infarction or coronary revascularization or hospitalization for other cardiac reasons (unstable or recurrent angina or heart failure), occurred in 111 patients (2.6%) without significant differences between those managed according to the GL recommendations and those that were not (2% vs. 3%, ns). There was also no significant difference in the incidence of the single components of MACE. Time to MACE was longer in patients managed according to the GL recommendations (106 days vs. 86 days, $P = 0.036$) mainly due to longer time to late revascularization (104 days vs. 66 days, $P = 0.028$) (*Table 4a*). Among QoL parameters, patients managed according to the GL recommendations showed a higher self-reported VAS score at baseline and even higher at follow-up (74 ± 20 vs. 72 ± 21, $P = 0.003$). Additional imaging tests were performed less frequently at follow-up in patients managed according to the GL recommendations as compared with their counterparts (5% vs. 7%, $P = 0.031$) (*Table 4b*).

Discussion

The present study shows that in a large population of patients enrolled in 24 European and non-European countries the 2019 ESC GL recommendations on the use of cardiac imaging tests for the diagnosis of CCS are frequently not adopted. The majority of the EURECA population consisted of patients without known CAD history and with an intermediate PTP (>5%) of obstructive CAD (66% of the whole population). Among these patients, those with a higher clinical likelihood of obstructive CAD (i.e. based on cardiovascular risk factors, typical angina, male sex, positive exercise ECG) were frequently directly referred to ICA without a previous imaging test, while a number of patients with a high PTP did not undergo any imaging test after a negative exercise ECG. On the other hand, 2019 ESC GL recommendations on the use of non-invasive imaging were frequently not adopted in patients with low PTP and a negative exercise ECG, for whom there is no indication for non-invasive imaging tests, and in patients with reduced LVEF, in whom ICA is indicated (*Figure 4*). Overall, referring patients to exercise ECG and ICA as first test were the main drivers of non-adoption of GL recommendations. Importantly, the adoption of GL recommendations was associated with a lower referral to ICA and a higher diagnostic yield of ICA and a higher percentage of ICA leading to revascularization procedures.

EURECA is the first registry on the use of cardiovascular imaging in CAD including different geographical regions in Europe and some non-EU countries with consistently different prevalence and risk for CAD,[2] as well as different health systems, and use of imaging modalities. Moreover, the registry started shortly after the release of 2019 GL[9] and this allowed the evaluation of the existing gap between

Table 3 Variables associated with the adoption of guideline recommendations for the overall diagnostic process 'endpoint b'

(Adoption of GL recommendations for 'endpoint b' could be defined in 4995/5156 patients)							
Variable	**% of missing data**	**Adoption of GL overall process (*N* = 2783)**	**Non-adoption of GL overall process (*N* = 2212)**	**Univariable analysis OR (95% CI)**	***P*-value**	**Multivariable analysis OR (95% CI)**	***P*-value**
Type of centres							
University Centre	2.2%	1897/2718 (69.79%)	1703/2166 (78.62%)	0.628 [0.551;0.716]	<0.001		
Departments							
Cardiovascular	2.2%	1785/2718 (65.67%)	1711/2166 (78.99%)	0.509 [0.447;0.580]	<0.001		
Demographic data							
Age (years)	0.0%	63.2 ± 11.4	64.0 ± 11.1	0.994 [0.989;0.999]	0.012	0.989 [0.982–0.996]	0.002
Female gender	0.0%	1280/2783 (45.99%)	719/2212 (32.50%)	1.768 [1.575;1.986]	<0.001	1.588 [1.356–1.859]	<0.001
Symptoms							
Typical angina	0.0%	590/2783 (21.20%)	738/2211 (33.38%)	0.537 [0.473;0.610]	<0.001		
CV risk factors							
Family history	11.4%	886/2561 (34.60%)	799/1865 (42.84%)	0.706 [0.624;0.798]	<0.001	0.837 [0.717–0.978]	0.025
Smoking	3.0%	1085/2714 (39.98%)	1000/2132 (46.90%)	0.754 [0.672;0.846]	<0.001		
Diabetes mellitus	0.7%	559/2768 (20.20%)	528/2192 (24.09%)	0.798 [0.697;0.913]	0.001		
Dyslipidemia	2.8%	1661/2730 (60.84%)	1446/2127 (67.98%)	0.732 [0.650;0.824]	<0.001	0.791 [0.672–0.931]	0.005
Hypertension	1.0%	1827/2763 (66.12%)	1603/2184 (73.40%)	0.707 [0.625;0.800]	<0.001		
Obesity	2.6%	709/2736 (25.91%)	634/2130 (29.77%)	0.825 [0.727;0.936]	0.003		
Previous CAD history							
Old myocardial infarction	1.8%	333/2735 (12.18%)	528/2172 (24.31%)	0.432 [0.371;0.502]	<0.001		
Previous revascularization	0.1%	430/2777 (15.48%)	736/2211 (33.29%)	0.367 [0.321;0.421]	<0.001	0.254 [0.209–0.307]	<0.001
LV function							
LVEF <50%	0.0%	130/2783 (4.67%)	120/2212 (5.42%)	0.854 [0.662;1.102]	0.225		
Exercise ECG							
Performed	0.0%	625/2783 (22.46%)	942/2212 (42.59%)	0.390 [0.345;0.441]	<0.001	0.696 [0.571–0.849]	<0.001
Integrated stress imaging							
Performed	0.0%	1623/2783 (58.32%)	475/2212 (21.47%)	5.116 [4.509;5.806]	<0.001	9.282 [7.551–11.409]	<0.001
CT coronary angiography							
Performed	0.0%	841/2783 (30.22%)	372/2212 (16.82%)	2.142 [1.866;2.458]	<0.001	3.372 [2.715–4.189]	<0.001
Invasive coronary angiography							
Performed	0.0%	420/2783 (15.09%)	1059/2212 (47.88%)	0.194 [0.169;0.221]	<0.001	0.253 [0.212–0.300]	<0.001

Integrated stress imaging: integrated variable expressing whether one non-invasive stress imaging test (any modality) was performed; CV, cardiovascular; CAD, coronary artery disease; LV, left ventricular.

current clinical practice and GL recommendations as well as the potential impact of clinical paths coherent with the new GL on patient management.

Population characteristics and management

The population characteristics (demographics, risk factors, ongoing treatment) mainly resembled those of most recent clinical imaging trials in CAD. Nevertheless, only 5% of patients without previous CAD and with normal LVEF had a PTP ≤5%, a relatively lower figure than that reported in the meta-analysis on which the current GL recommendations are based.[13] The higher proportion of academic tertiary centers participating in the EURECA registry, to which subjects at relatively higher risk are preferentially referred, possibly explain the composition of our population.

The clinical diagnosis of obstructive CAD and of inducible ischaemia were posed in 24% and 19% of the overall population, which compares well with the low prevalence reported in other imaging trials.[10,15,18–20] The prevalence of obstructive CAD (coronary stenosis >70% in at least one epicardial vessel) documented on ICA and high-risk ischaemia was even lower, in the range of 13% and 9%, respectively. Interestingly, these results indirectly confirm, in a multiethnic and heterogeneous population, the downgrading of PTP estimation of obstructive CAD prevalence by the new predictive model used in the 2019 GL.[9,12,13] The prevalence of non-obstructive CAD was high and was not predicted by the PTP estimation. Revascularization was performed only in 13% of all patients but current medical treatment was modified in a larger proportion of patients probably driven by the recognition of both obstructive and non-obstructive CAD as well as of inducible ischaemia by imaging.[21,22]

Table 4a Events at follow-up in patients managed adopting or non-adopting guideline recommendations

(Adoption of GL recommendations defined for the overall diagnostic process, endpoint b)				
Variable	**Whole follow-up population N = 4262 (100%)**	**Subgroup adoption of GL N = 2514 (59.0%)**	**Subgroup non-adoption of GL N = 1748 (41.0%)**	***P*-value**
Follow-up events				
MACE	111/4262 (2.6%)	58/2514 (2.3%)	53/1748 (3.0%)	0.144
Time to MACE (days) Missing = 109	96.0 (47.0;147.0)	106.0 (67.0;176.5)	86.0 (32.0;119.0)	0.036
Cardiac death or non-fatal myocardial infarction	16/4262 (0.4%)	10/2514 (0.4%)	6/1748 (0.3%)	0.775
Time to cardiac death or non-fatal myocardial infarction Missing = 16	144.0 (49.5;191.0)	154.0 (106.0;207.0)	89.5 (5.0;164.0)	0.175
Cardiac death	5/4262 (0.1%)	2/2514 (0.1%)	3/1748 (0.2%)	0.406
Time to cardiac death (days) Missing = 5	106.0 (52.0;161.0)	133.5 (106.0;161.0)	52.0 (1.0;164.0)	0.564
Non-fatal myocardial infarction	12/4262 (0.3%)	8/2514 (0.3%)	4/1748 (0.2%)	0.771
Time to non-fatal myocardial infarction (days) Missing = 12	144.0 (26.0;204.0)	174.0 (94.0;207.5)	66.0 (2.5;154.0)	0.106
Coronary revascularization	59/4262 (1.4%)	35/2514 (1.4%)	24/1748 (1.4%)	0.958
Time to coronary revascularization (days) Missing = 59	91.0 (30.0;142.0)	104.0 (41.0;172.0)	65.5 (11.5;99.0)	0.028
Hospitalization for other cardiac reasons	81/4262 (1.9%)	42/2514 (1.7%)	39/1748 (2.2%)	0.187
Time to hospitalization for other cardiac reasons (days) Missing = 78	97.0 (68.0;134.0)	106.0 (74.0;181.0)	93.0 (59.0;124.0)	0.080
All cause death	12/4262 (0.3%)	8/2514 (0.3%)	4/1748 (0.2%)	0.771
Time to all cause death (days) Missing = 12	113.0 (53.5;157.0)	113.0 (61.0;157.0)	93.5 (26.5;149.5)	0.610
Hospitalization for any reason	189/4262 (4.4%)	103/2514 (4.1%)	86/1748 (4.9%)	0.199
Time to hospitalization for any reason (days) Missing = 186	107.0 (60.0;165.0)	112.0 (65.0;184.0)	99.5 (59.0;151.0)	0.151

MACE: cardiac death or non-fatal myocardial infarction or coronary revascularization or hospitalization for other cardiac reasons; Hospitalization for other cardiac reasons: hospitalization for unstable angina or recurrent angina or heart failure.

Table 4b Quality of life, symptoms and additional testing at follow-up in patients managed adopting or non-adopting guideline recommendations

(Adoption of GL recommendations defined for the overall diagnostic process, endpoint b)				
Variable	**Whole follow-up population *N* = 4262 (100%)**	**Subgroup adoption of GL *N* = 2514 (59.0%)**	**Subgroup non-adoption of GL *N* = 1748 (41.0%)**	***P*-value**
Baseline quality of life				
Quality of Life Questionnaire—VAS Score (self-reported)Missing = 802	70.9 (±19.1)	71.4 (±19.1)	70.3 (±19.0)	0.036
Quality of Life Questionnaire—Index Score (cTTO model) Missing = 748	0.8 (±0.2)	0.8 (±0.2)	0.8 (±0.2)	0.238
Follow-up quality of life				
Quality of Life Questionnaire—VAS Score (self-reported)Missing = 1209	72.8 (±20.6)	73.7 (±20.2)	71.6 (±21.0)	0.003
Quality of life Questionnaire—Index Score (cTTO model) Missing = 1207	0.8 (±0.2)	0.8 (±0.2)	0.8 (±0.2)	0.138
Follow-up change in symptoms				
Symptoms unchanged or worsenedMissing = 89	1483/4173 (35.5%)	852/2475 (34.4%)	631/1698 (37.2%)	0.070
Follow-up additional imaging testing				
Any additional imaging testing	239/4262 (5.6%)	125/2514 (5.0%)	114/1748 (6.5%)	0.031
Stress imaging	148/4262 (3.5%)	77/2514 (3.1%)	71/1748 (4.1%)	0.080
CTCA	11/4262 (0.3%)	5/2514 (0.2%)	6/1748 (0.3%)	0.375
Invasive coronary angiography	98/4262 (2.3%)	50/2514 (2.0%)	48/1748 (2.7%)	0.105

Use of imaging and adoption of GL recommendations

Both the 2019 ESC GL on CCS[9] and the 2021 ACC/AHA GL for the evaluation and diagnosis of chest pain[23] recommend performing non-invasive imaging tests, either by CTCA or stress imaging, in patients with intermediate or high PTP to recognize the individuals that would benefit from a more targeted management. In addition, both GL do not recommend the performance of unhelpful testing in patients with low clinical likelihood of obstructive CAD.

In the EURECA registry, most participating centres had access to at least two non-invasive stress imaging modalities (81%) and CTCA (93%). Despite this, the actual use of non-invasive imaging was lower than that recommended by GL and there was no direct relationship with the availability of tests. More importantly, while ICA and FFR/iFR were similarly available in most centres (94% and 85%), FFR/iFR measurements were performed only in one of 13 patients undergoing ICA.

The diagnostic process did not adopt the ESC GL recommendations in 44% of patients. The analysis of the major predictors of discrepancy between current practice and GL recommendations revealed that the main drivers of non-adoption of GL recommendations were the use of exercise ECG instead of non-invasive imaging tests and the direct referral of a substantial number of patients to ICA. No imaging use was more frequent in patients with lower PTP and lower clinical risk. On the other hand, ICA was performed as a first test (i.e. not preceded by non-invasive imaging) more frequently in patients with higher PTP and perceived risk. Moreover, even when ICA was not associated with any other imaging functional test, FFR or iFR (recommended by current guidelines) were rarely measured, similarly to other registries.[24,25] There are multiple potential explanations for this clinical practice including easier access and short waiting times for exercise ECG and invasive procedures in cardiovascular departments, in some centres and countries, as compared with referral of patients to imaging departments which are frequently separated and with longer waiting lists. In addition, there is probably a still common understanding that demonstration of obstructive CAD on ICA and immediate revascularization may save time, costs, and may translate into a better outcome particularly in patients at higher risk, even though this contrasts with the results of clinical trials.[18,26,27] This practice likely resulted in the lower diagnostic yield of ICA[28] and in the even lower proportion of ICA leading to revascularization in patients managed not according to GL recommendations.

The use of non-invasive imaging tests was not always in agreement with the ESC GL. In 53% of patients with a PTP <5% either CTCA (23%) or stress imaging (24%) were performed. This is not in agreement with the 2019 GL, but we should consider that most of these patients would have been classified as intermediate risk using the Genders model included in the 2013 GL,[29] which were possibly still influencing clinical practice in the EURECA registry. Moreover, recent studies have promoted the use of CTCA as first strategy in patients with suspected CCS independently of PTP estimation and even in patients at

very low risk.[10,20] On the other hand, CTCA has been used in a substantial proportion of patients with previous CAD and/or revascularization (13%) in whom current GL do not consider this test the most appropriate imaging technique (particularly considering the technical challenges that these clinical scenarios pose).[9] In addition, in a variable proportion (7 to 36%) of patients undergoing a first non-invasive imaging exam, the subsequent diagnostic process was not coherent with the results of the test (see Supplementary material online, *Figures S2 and S3*).

The effects of adopting the ESC GL recommendations in downstream management of patients were substantial as demonstrated by (i) lower referral to diagnostic ICA (15% vs. 48%); (ii) lower revascularization procedures performed (8% vs. 19%); (iii) higher diagnostic yield of ICA for obstructive CAD (>70% stenosis) (60% vs. 39%); and (iv) higher proportion of ICA leading to coronary revascularization (54% vs. 37%).

The MACE rate was 2.6% at a median 172 days of follow-up. Cardiac death or non-fatal myocardial infarction occurred in 0.4% of patients, potentially translating into a 8% 10-year risk of fatal and non-fatal events, which defines a high cardiovascular risk population.[2] Other follow-up events included hospitalization for other cardiac reasons (2%) and late revascularizations (1%) in line with previous studies.[15,20,22] The relatively short follow-up precludes robust conclusions about the potential impact of GL-based diagnostic strategies on major events. Actually, the MACE rate at 6 months was not different between the patients in whom the diagnostic path adopted the GL recommendations vs. those in whom the diagnostic path did not adopt the GL. On the other hand, the adoption of GL recommendations led to significantly lower rate of invasive procedures at baseline, a significantly better patients' perceived QoL, fewer additional tests, and a longer time to late coronary revascularizations at follow-up, underscoring potential advantages of an early management adopting GL recommendations.

Limitations

Of the 5156 patients enrolled, complete data to evaluate adherence were available in 5006 (97%) for 'endpoint a' and in 4995 pts (97%) for 'endpoint b' mainly due to tests scheduled but not performed for unspecified intercurrent reasons. The estimation of PTP of obstructive CAD, based on reported age, sex, and symptoms, was used to define the adoption of the GL recommendations, while clinical likelihood could not be estimated, despite the availability of some 'modifying' variables. Among these, the results of ECG, when performed, were considered as a potential modifier in patients with PTP ≤5% or with 5%<PTP ≤ 15%. Nevertheless, the contribution of other modifiers, such as risk factors, to the management choices could not be taken into account due to the lack a specific algorithm in the GL. Moreover, investigators may have used some discretion in interpreting the GL for the use of imaging in specific patients, but this could not be taken into account in the data analysis. The choice of specific paths (i.e. use of ICA without a previous non-invasive imaging test) could have been variably influenced by investigators' and/or patients' preferences, local habits and availability of resources. The analysis of the contribution of these variables was, however, beyond the purposes of the present study. The final diagnosis assessment was based on that reported by the investigators evaluating the complete diagnostic process based on previously defined general criteria, thus the disease categories may not necessarily correspond to the specific results of each diagnostic modality. Nevertheless, this was an intentional choice to more strictly reflect the clinical judgement, which had guided downstream management. Despite the registry included 73 centres from 24 countries, mainly academic tertiary centers have been included and these could not be fully representative of all daily clinical practices. Moreover, some relevant European countries were not represented and only three non-European countries were included. However, patients from all the four major European risk areas recently redefined were enrolled.[2] Very different health systems were also represented in the EURECA registry so that costs and reimbursement policy could have affected the diagnostic pathways. As a matter of fact, the rate of adoption of GL recommendations was different in different geographical areas (see Supplementary material online, *Figure S5*). A specific health-economic and country-specific analysis would be needed to address this issue more correctly but it was beyond the purposes of the present study. Finally, the enrolment period was coincident with the outbreak of the COVID-19 pandemic and 22% of the patients were enrolled or had to complete the diagnostic work-up after February 2020. The sensitivity analysis performed in patients managed after the pandemic outbreak showed some differences in management as compared with that before the outbreak, in particular with an even lower use of stress imaging and CTCA in favour of ICA as first test. The restriction in the use of some imaging modalities (in particular stress tests), as well as the prolongation of the waiting lists, could have somewhat conditioned these practices. Regarding dichotomized variables included in the univariable and multivariable analyses, patients with missing data were not taken into account. The rate of missing data was ≤3% for all the variables except for body mass index (10% of patients) and for 'family history of CAD' (11% of patients). Body mass index was not included in the multivariable models. Family history of CAD was included since it was a significant predictor of adoption of GL recommendations while the proportion of missing data was not considered as affecting the results.

Conclusions

The EURECA registry confirmed that the prevalence of obstructive CAD and of significant ischaemia in a contemporary population of patients with stable chest pain is relatively low (24% and 19%, respectively). Importantly, the registry showed that non-obstructive CAD is a frequent (38%), underlying pathologic substrate in these patients. Furthermore, it demonstrated that in current clinical practice GL recommendations for the diagnostic process of CCS are still not completely adopted mainly due to a frequent use of exercise ECG and ICA without performing any non-invasive anatomical or functional imaging or functional invasive assessment of CAD. It also evidenced that non-adoption of GL recommendations is associated with a higher number of relatively unnecessary ICAs, a lower diagnosis of patients at high risk, a higher use of additional testing, and a shorter time to late revascularization procedures at follow-up.

Whether a clinical practice that adopts current international GL recommendations could improve risk stratification in patients with stable chest pain and whether this practice would translate into lower costs, lesser risk, and more clinical benefits for patients with CCS will deserve additional studies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data underlying this article are subject to an embargo of 12 months from the publication date of the article. Once the embargo expires, the data will be available upon reasonable request to the EORP EURECA Executive Committee Chair, with the approval of the EORP Oversight Committee.

Appendix

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EORP Team

C. Arsac, C. Berle, G. Chhabra, C. Laroche, P-A. Mcneill, Y. Song, M-E. Sozmen, C. Taylor, W-A. Zabré.

National Coordinators

C. Anagnostopoulus, GR; G. Barone Rochette, FR; R.R. Buechel, CH; J. Celutkiene, LT; B. Cosyns, BE; S. Dodic, RS; T. Edvardsen, NO; H. Engblom, SE; A. Gimelli, IT; S. Graf, AT; M. Gyongyosi, AT; M. Haertel Miglioranza, BR; F. Macedo, PT; N. Maroz-Vadalazhskaya, BY; P. Maurovich-Horvat, HU; D. Muraru, IT; F. Paleev, RU; E. Plonska-Gosciniak, PL; T. Podlesnikar, SI; B.A. Popescu, RO; A. Saad, EG; L.E. Sade, TR; A. Saraste, FI; A. Scholte, NL; C-H. Sia, SG; J.L. Zamorano, ES.

The EURECA Investigators

Austria: *Vienna:* M. Gyongyosi, S. Graf, A. Spannbauer, E. Han, C. Muller, **Belarus:** *Brest City:* A. Radziyeuskaya, K. Rakhatsevich, M. Kauhanka, *Grodno:* L. Badziukova, E. Kolva, O. Zhuk, S. Hryb, *Minsk:* N. Maroz-Vadalazhskaya, A. Zakharevich, **Belgium:** *Jette:* B. Cosyns, A. Azzano, B. Vandeloo, B. Roosens, C. Weytjens, D. Plein, D. Schoors, I. Lemoine, J-F. Argacha, K. Van Den Bussche, L. Soens, S. Lochy, S. Droogmans, **Brazil:** *Curitiba-Parana:* J. Vitola, M. Morita, R. Cerci, E. De Paula, *Porto Alegre:* M. Haertel Miglioranza, P.A.M. Cella, J.L.d.C. Vieira, L. Birk, R.B. Guimarães, D.H. Terra, **Egypt:** *Zagazig:* A. Saad, M. Ali, **Finland:** *Turku:* J. Airaksinen, A. Saraste, C. Paunonen, K. Lahtonen, T. Vasankari, **France:** *Grenoble:* G. Barone Rochette, J. Hildt, C. Charlon, *Paris:* F. Hyafil, F. Scalbert, R. Chequer, F. Rouzet, *Toulouse:* O. Lairez, A. Blanc, D. Dang, E. Cariou, K. Sanchis, J. Larroche, M. Lemasle, P. Pascal, P. Revel-Mouroz, S. Cazalbou, S. Sayir, V. Blanchard, V. Houard, Y. Lavie-Badie, **Greece:** *Athens:* I. Ikonomidis, K. Katogiannis, *Athens:* A. Marsonis, A. Manginas, M. Boutsikou, *Thessaloniki:* I. Styliadis, E. Moralidis, S. Sotiriou, V. Sachpekidis, **Hungary:** *Budapest:* P. Maurovich-Horvat, M. Boussoussou, F. Suhai, M. Kolossváry, A. Jermendy, S. Borzsák, J. Simon, B. Szilveszter, J. Csore, B. Vattay, M. Vecsey-Nagy, *Szeged:* R. Sepp, A. Thury, Á. Séllei, A. Farkas, A. Farkas, B. Polestyuk, F. Tamás Nagy, R. Csadi, **Italy:** *Bari:* S. Favale, A.I. Guaricci, A. Scardapane, F.V. Napoli, M.E. Lepera, R. Ruggieri, V. Marangelli, T. Achille, *Florence:* N. Marchionni, N. Carrabba, A. Migliorini, R. Valenti, N. Ceschia, F. Ciatti, *Genoa:* L. Castellan, S. Seitun, M. Baucknehtt, C. De Lorenzi, I. Porto, P. Ameri, G. Sambuceti, F. Pescetelli, *Lido Di Camaiore:* G. Casolo, J. Del Meglio, R. Poddighe, *Mestre-Venice:* F. Rigo, V. Spadotto, *Milan:* A. Moreo, A. Milazzo, B. De Chiara, F. Musca, F. Casadei, G. Quattrocchi, G.M. Santambrogio, O.E. Belli, P. Pedrotti, P. Sormani, P.A. Merlini, F. Spano, J. Sun, M. Palazzini, *Milan:* G. Pontone, M. Guglielmo, S. Scafuri, *Milan-Rozzano:* G. Condorelli, A. Rossi, F. Fazzari, *Milano:* G. Parati, A. Giuliano, N. Tanese, V. Guida, G. Branzi, *Naples:* P. Perrone-Filardi, S. Paolillo, P. Gargiulo, I. Esposito, S. Dell Aversana,

F. Marsico, *Parma:* N. Gaibazzi, S. Suma, *Pisa:* R. De Caterina, F. Lattanzi, D. Morrone, R. Liga, U. Conti, *Pisa:* D. Chiappino, M. Emdin, S. Berti, A. Gimelli, A. Decaterina, A. Clemente, A. Giannoni, A. Barison, D. Neglia, E. Pasanisi, M. Coceani, V. Spini, *Rome:* G.A. Lanza, V. Melita, E. Ravenna, A. De Vita, *Rome:* M. Mancone, F. Infusino, G. Montefusco, M. Tocci, N. Salvi, *Rome:* P.G. Pino, L. Genuardi, C. Manzara, P. Celli, *Sassari:* G.D. Sanna, G. Parodi, F. Dossi, A. Marini, *Siena:* M. Cameli, G.E. Mandoli, F. Contorni, *Trieste:* G. Faganello, S. Furlotti, A. Porcari, L. Pagura, M. Zaccari, V. Nuzzi, **Lithuania:** *Kaunas:* J.J. Vaskelyte, R. Zvirblyte, E. Sakaviciute, R. Virsinskaite, *Vilnius:* J. Celutkiene, L. Balkeviciene, E. Dvinelis, **Netherlands:** *Leiden:* A. Scholte, M. Van Hout, **Norway:** *Oslo:* T. Edvardsen, J. Tangen, K. Melberg, M. Ribe, **Poland:** *Katowice:* K. Golba, K. Goscinska-Bis, *Poznan:* A. Szyszka, R. Dankowski, *Szczecin:* E. Plonska-Gosciniak, M. Stepien, P. Piatek, K. Bedkowski, **Portugal:** *Coimbra:* R. Teixeira, C. Saleiro, J. Lopes, J. Sousa, A. Pais, *Guimaraes:* M. Fernandes, A. Lourenco, F. Cardoso, F. Ferreira, J. Portugues, *Lisbon:* A. Almeida, A. Nunes-Ferreira, A. Veiga, C. David, D. Caldeira, G. Cantinho, N. Cunha, T. Rodrigues, *Porto:* F. Macedo, M. Paiva, C. Sousa, X. Resende, M. Vasconcelos, P. Diogo, M. Martins de Carvalho, *Setúbal:* L. Mendes, C. Reis, I. Melo, J. Patinha, J. Santos, M. Castro, P. Amado, R. Rodrigues, S. Balão, S. Lima, V. Madeira, **Romania:** *Targu Mures:* T. Benedek, A. Mester, D. Opincariu, I. Rodean, I.S. Benedek, M. Ratiu, R. Hodas, R. Licu, **Russian Federation:** *Ivanovo:* S. Rachkova, M. Krotova, O. Belova, *Kemerovo:* A. Sumin, A. Kokov, E. Gorbunova, O. Polikutina, E. Korok, A. Korotkevich, A. Shcheglova, O. Lebedeva, *Moscow:* A. Basinkevich, F. Ageev, D. Bubnov, Z. Blankova, M. Subotnikov, S. Efindeeva, S. Gavrushina, T. Polanskaya, E. Kozlova, E. Nuraliev, T. Kolmakova, N. Shamrina, L. Smirnova, E. Orlova, A. Sonina, A. Loginova, L. Zhigunova, M. Smirnova, A. Osokina, E. Korobova, E. Tsagareishvili, O. Svirida, P. Dergousov, A. Borisov, M. Kuznetsova, G. Silvestrova, L. Kotova, K. Gavrilova, T. Fofanova, R. Guchaev, M. Vitsenya, Y. Merzlikina, N. Zhukova, R. Kaziev, V. Gazizova, *Ryazan:* E. Filippov, K. Moseichuk, *Tomsk:* K. Zavadovsky, A. Boshchenko, K. Kopeva, A. Mochula, A. Maltseva, E. Grakova, **Serbia:** *Belgrade:* A. Djordjevic Dikic, B. Beleslin, N. Boskovic, M. Petrovic, V. Giga, S. Dedic, *Sremska Kamenica:* S. Dodic, D. Dabovic, A. Ilic, M. Bjelobrk, M. Cankovic, M. Jarakovic, I. Tomas, S. Bjelic, S. Tadic, T. Miljkovic, T. Popov, **Singapore:** *Singapore:* C-H. Sia, R. Ching-Chiew Wong, K-K. Poh, W.K. Kong, **Slovenia:** *Ljubljana:* T. Podlesnikar, B. Berlot, M. Stalc, H. Maiga, B. Guzic Salobir, J. Ambrozic, M. Jovanovic, M. Mrak, M. Skafar, J. Toplisek, A. Ovsenik, M. Bervar, M. Dolenc, N. Pavsic, B. Segulin, M. Rauber, M. Cvijic, L. Vitez, B. Jug, P. Berden, R. Zbacnik, **Spain:** *A Coruna:* A. Bouzas-Mosquera, J. Peteiro, *Barcelona:* S. Aguadé-Bruix, C. Espinet Coll, N. Pizzi, *Leon:* D. Alonso Rodríguez, A. Martin Centellas, *Madrid:* B. Terol, I. Ponz, T. Lopez, *Santiago de Compostela:* M-A. Martinez Monzonis, B. Diaz Fernandez, C. Cacho Antonio, A. Torrelles Fortuni, M. Perez Dominguez, A. Garcia Campos, J. Lopez Pais, **Sweden:** *Lund:* H. Engblom, A. Sakaria, P. Jarnhall, **Switzerland:** *Zürich:* R.R. Buechel, **Turkey:** *Ankara:* L.E. Sade, U. Abbas Bal, E. Karacaglar, U. Abbas, *Canakkale:* A. Barutcu, M. Arslan, *Istanbul:* D. Ural, G. Aslan, E. Yurtseven, *Istanbul:* B. Uygur, C. Yildirim, B. Corekcioglu, *Izmir:* E. Ozpelit, H. Kakar, *Kocaeli:* A. Erkol, D. Kaptan Ozen, B. Turan, *Kocaeli:* B. Acar, *Pamukkale:* S. Yilmaz.

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