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EURObservational Research Programme: the Chronic Ischaemic Cardiovascular Disease Registry: Pilot phase (CICD-PILOT)

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Aims Chronic ischaemic cardiovascular disease (CICD) is a major cause of mortality and morbidity worldwide. The primary objective of the CICD-Pilot registry was to describe the clinical characteristics and management modalities across Europe in a broad spectrum of patients with CICD.

Methods and results The CICD-Pilot registry is an international prospective observational longitudinal registry, conducted in 100 centres from 10 countries selected to reflect the diversity of health systems and care attitudes across Europe. From April 2013 to December 2014, 2420 consecutive CICD patients with non-ST-elevation acute coronary syndrome ($n = 755$) and chronic stable coronary artery disease ($n = 1464$), of whom 933 (63.7%) were planned for elective coronary intervention, or with peripheral artery disease (PAD) ($n = 201$), were enrolled (30.5% female patients). Mean age was 66.6 $\pm$ 10.9 years. The following risk factors were reported: smoking 54.6%, diabetes mellitus 29.2%, hypertension 82.6%, and hypercholesterolaemia 74.1%. Assessment of cardiac function was made in 69.5% and an exercise stress test in 21.2% during/within 1 year preceding admission. New stress imaging modalities were applied in a minority of patients. A marked increase was observed at discharge in the rate of prescription of angiotensin-converting enzyme-inhibitors/angiotensin receptor blockers (82.8%), beta-blockers (80.2%), statins (92.7%), aspirin (90.3%), and clopidogrel (66.8%). Marked differences in clinical profile and treatment modalities were observed across the four cohorts.

Conclusion The CICD-Pilot registry suggests that implementation of guideline-recommended therapies has improved since the previous surveys but that important heterogeneity exists in the clinical profile and treatment modalities in the different cohorts of patients enrolled with a broad spectrum of CICDs.

Keywords Stable angina • Ischaemic cardiovascular disease • Management • Drug therapy • Cardiac procedures

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Introduction

Coronary artery disease (CAD) remains the first cause of death worldwide and is a major burden for healthcare systems.[1,2] It is expected to remain the leading cause of mortality and morbidity in 2020 despite considerable progress in diagnosis and treatment.[3]

The landscape of CAD diagnosis and management has considerably changed with new stress imaging modalities for the diagnosis, improved prevention measures, and more efficient revascularization therapies, whereas ageing populations are more prone to develop the disease and are therefore at high risk of myocardial infarction, sudden cardiac death, or heart failure. Scientific societies such as the European Society of Cardiology (ESC), the American College of Cardiology, and the American Heart Association have recently updated their recommendations accordingly.[4,5]

In addition, important geographic variations in presentation, risk factors, and diagnostic modalities have been identified in a previous European survey on patients with stable angina presenting to European cardiologists. However, this survey did not include any follow-up and was therefore unable to assess whether clinical outcomes are influenced by geographic variations or not.[6]

In this context, it is important to reassess in a contemporary environment the clinical profile and the diagnostic and treatment strategies of a broad spectrum of patients with chronic ischaemic cardiovascular disease (CICD).

As atherosclerosis is a systemic disease, it is also important that physicians appreciate the importance of detecting atherosclerosis in other vascular beds than the coronary circulation and, as shown in the Reduction of Atherosclerosis for Continued Health (REACH) Registry, a substantial percentage of patients with chronic CAD have indeed frequently cerebrovascular disease, low extremity artery disease, or both.[7]

The purpose of the CICD registry is therefore to characterize CICD including patients with peripheral artery disease (PAD) in terms of demographic characteristics, clinical profiles management, and outcomes and to identify inter-regional differences and potential gaps between actual treatment and evidence-based recommendations in participating countries.

The CICD-Pilot phase is aimed at validating the structure, performance, feasibility, and quality of the data set, with the intention of extending the survey to other participating ESC countries into a long-term registry.

Baseline characteristics and treatment modalities of patients recruited in the 10 participating countries are described in this article.

Methods

Study design

The CICD-Pilot survey is an international prospective observational longitudinal registry in CAD and/or PAD patients with 3-year follow-up.

The study has been approved by local Institutional Review Boards, and all patients gave informed consent in accordance with national and local regulations. Patients were recruited in 100 centres from 10 countries selected on the basis of geographic distribution:

- two Western European countries (France and Germany, 20 centres, $n = 405$ patients);
- two Northern (Latvia and Lithuania, six centres, $n = 404$ patients);
- three Eastern (Poland, Romania, and Russian Federation, 45 centres, $n = 1025$ patients);
- three Southern (Greece, Italy, and Portugal, 29 centres, $n = 586$ patients).

The National Cardiac Societies of each participating country agreed to participate in the programme and were asked to select centres able to recruit patients for four different cohorts:

- *Cohort 1*: consecutive patients with chronic CAD and non-ST elevation acute coronary syndrome undergoing a percutaneous coronary intervention (PCI) within 72 h from symptom onset, enrolled in the catheterization laboratory (ACS PCI group);
- *Cohort 2*: consecutive patients with chronic stable CAD undergoing elective coronary intervention enrolled in the catheterization laboratory (elective PCI group);
- *Cohort 3*: stable CAD patients enrolled in general hospitals and clinics without interventional and cardiovascular surgery facilities (stable CAD group);
- *Cohort 4*: consecutive patients with peripheral artery interventions (PAD group).

The theoretical number of participating centres for each country was decided according to the population of each country: one centre with interventional facilities per two million inhabitants for cohorts 1 and 2, with a maximum of 30 centres per country and about 15–30 centres per country for cohort 3. Centres performing more than 30 procedures per year were selected to recruit in cohort 4. However, the actual number of centres was lower than expected, and overall one hundred centres took part in the survey. Each centre was asked to enrol at least 20 consecutive patients.

Local monitoring visits were performed to check the quality of the collected data and the consecutiveness of enrolment in a sample of centres chosen on a monitoring risk-based strategy.

The survey was conducted by an independent executive committee (Appendix), responsible for the formulation and implementation of the study protocol.

A steering committee, composed of two co-chairpersons of the executive committee and of each national coordinator of the study, was created in order to ensure national feedback on the protocol and proper implementation of the survey at the national level.

The EURObservational Research Programme (EORP) department of the ESC was appointed to (i) coordinate the project and the operations of the CICD-Pilot; (ii) provide support to the committees, national coordinators, and participating centres; and (iii) ensure quality control of data and study procedure.

This survey was approved by each local or national Institutional Review Board according to the national regulations of each participating country. No data were collected before detailed information was provided to the patient, and a signed informed consent was obtained.

The database was set up at the European Heart House, according to the requirements defined by the Executive Committee, and the statistical analyses were performed by the EORP Department.

Statistical analysis

Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean $\pm$ SD and/or as median and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Among-group comparisons were made using a χ^2 test or a Fisher's exact test if any expected cell count was less than five.

A two-sided *P*-value less than 0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

From April 2013 to December 2014, 2420 patients were enrolled: 755 in ACS PCI, 933 in elective PCI, 531 in stable CAD, and 201 in PAD.

Ten patients did not provide consent and are therefore not included in the database.

Clinical profile of the patients

The baseline characteristics of the overall population and of the four individual cohorts are provided in *Table 1*.

Mean age was 66.6 years and was slightly higher in patients enrolled in ACS PCI or elective PCI cohorts than in stable CAD and PAD cohorts. Female patients accounted for 30.5% of the patients. Diabetes mellitus was reported in 29.2% of the patients and was more prevalent (49.3%) in cohort 4. Smoking (current/former) was observed in 54.6% of the patients and was highly prevalent in cohorts 1 (60.4%) and 4 (64.7%).

A history of hypertension was reported in 82.6% of the cases and of hypercholesterolaemia in 74.1%. About 16.6% of the female patients and 51.4% of the male patients had an age of <55 (females) and <60 years (males) at the time of first cardiovascular disease manifestation. Mean systolic blood pressure was higher in the PAD patients than in those from the other three cohorts.

A history of previous ST elevation acute coronary syndrome (STEMI) and non-ST elevation acute coronary syndrome (NSTEMI)

Table 1 Demographics and other baseline characteristics by cohort

	Cohort, all	Cohort 1, ACS PCI	Cohort 2, elective PCI	Cohort 3, stable CAD	Cohort 4, PAD	*P*-value
No. of patients	2420	755	933	531	201	
Age at inclusion						
N	2420	755	933	531	201	0.0087
Mean ± SD	66.6 ± 10.9	66.0 ± 11.7	66.2 ± 10.1	67.3 ± 11.2	68.6 ± 10.6	
Median (IQR)	67.0 (59.0–75.0)	66.0 (58.0–75.0)	66.0 (59.0–74.0)	67.0 (59.0–76.0)	70.0 (60.0–76.0)	
Female gender	739/2420 (30.5%)	242/755 (32.1%)	266/933 (28.5%)	181/531 (34.1%)	50/201 (24.9%)	0.0318
SBP (mmHg)						
N	2414	755	933	528	198	0.0002
Mean ± SD	136.5 ± 20.2	137.7 ± 22.0	135.4 ± 17.7	134.7 ± 21.0	141.3 ± 21.3	
Median (IQR)	134.0 (120.0–150.0)	136.0 (120.0–150.0)	132.0 (120.0–147.0)	130.0 (120.0–148.0)	140.0 (130.0–155.0)	
HR (b.p.m.)						
N	2419	755	932	531	201	<0.0001
Mean ± SD	70.4 ± 13.1	73.3 ± 13.7	67.6 ± 10.6	71.4 ± 15.3	70.1 ± 12.0	
Median (IQR)	70.0 (61.0–77.0)	71.0 (64.0–80.0)	67.0 (60.0–73.0)	70.0 (62.0–78.0)	70.0 (60.0–76.0)	
Diabetes mellitus	706/2420 (29.2%)	215/755 (28.5%)	254/933 (27.2%)	138/531 (26.0%)	99/201 (49.3%)	<0.0001
Smoking status	1321/2420 (54.6%)	456/755 (60.4%)	465/933 (49.8%)	270/531 (50.8%)	130/201 (64.7%)	<0.0001
Hypertension	1998/2420 (82.6%)	605/755 (80.1%)	785/933 (84.1%)	434/531 (81.7%)	174/201 (86.6%)	0.0659
Hypercholesterolaemia	1793/2419 (74.1%)	522/755 (69.1%)	735/932 (78.9%)	383/531 (72.1%)	153/201 (76.1%)	<0.0001
Previous NSTE ACS	488/2420 (20.2%)	167/755 (22.1%)	166/933 (17.8%)	142/531 (26.7%)	13/201 (6.5%)	<0.0001
Previous STEMI ACS	594/2420 (24.5%)	156/755 (20.7%)	291/933 (31.2%)	125/531 (23.5%)	22/201 (10.9%)	<0.0001
Previous peripheral revascularization	142/2420 (5.9%)	28/755 (3.7%)	30/933 (3.2%)	17/531 (3.2%)	67/201 (33.3%)	<0.0001
Chronic kidney disease	275/2397 (11.5%)	85/746 (11.4%)	86/928 (9.3%)	71/523 (13.6%)	33/200 (16.5%)	0.0085
Previous stable CAD	1633/2420 (67.5%)	335/755 (44.4%)	794/933 (85.1%)	427/531 (80.4%)	77/201 (38.3%)	<0.0001
Previous revascularization (PCI/CABG)	998/1633 (61.1%)	227/335 (67.8%)	455/794 (57.3%)	257/427 (60.2%)	59/77 (76.6%)	0.0003
Previous cerebrovascular disease	396/2420 (16.4%)	83/755 (11.0%)	133/933 (14.3%)	91/531 (17.1%)	89/201 (44.3%)	<0.0001
Chronic obstructive pulmonary disease	165/2370 (7.0%)	52/738 (7.0%)	48/912 (5.3%)	41/522 (7.9%)	24/198 (12.1%)	0.0050

SD, standard deviation; IQR, interquartile range; SBP, systolic blood pressure; HR, heart rate; STE ACS, ST elevation acute coronary syndrome; NSTE ACS, non-ST elevation acute coronary syndrome; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table 2 Investigations during admission/consultation or within 1 year by cohort

	Cohort, all	Cohort 1, ACS PCI	Cohort 2, elective PCI	Cohort 3, stable CAD	Cohort 4, PAD	*P*-value
No. of patients	2420	755	933	531	201	
S-creatinine (mg/dL)						
N	2341	732	892	517	200	0.0296
Mean ± SD	1.15 ± 2.68	1.06 ± 0.72	1.05 ± 0.78	1.43 ± 5.51	1.16 ± 0.91	
Median (IQR)	0.94 (0.80–1.15)	0.93 (0.78–1.16)	0.94 (0.80–1.10)	0.97 (0.83–1.20)	0.97 (0.80–1.15)	
Fasting glucose (mg/dL)						
N	2149	701	773	476	199	<0.0001
Mean ± SD	116.20 ± 44.02	124.02 ± 47.46	109.90 ± 38.99	110.10 ± 37.85	127.73 ± 55.68	
Median (IQR)	103.00 (91.00–125.33)	110.00 (95.16–137.00)	99.00 (89.00–117.00)	100.00 (90.00–114.83)	109.67 (94.00–145.00)	
C-reactive protein (mg/dL)						
N	1089	446	307	242	94	0.0185
Mean ± SD	8.54 ± 25.69	10.98 ± 32.39	6.24 ± 23.82	7.36 ± 15.27	7.48 ± 13.49	
Median (IQR)	2.40 (1.00–6.40)	3.05 (1.00–7.70)	2.20 (1.00–5.00)	1.70 (0.80–5.60)	2.84 (1.00–7.00)	
LDL (mg/dL)						
N	1946	639	686	452	169	<0.0001
Mean ± SD	101.7 ± 42.7	110.4 ± 44.8	100.7 ± 43.1	94.9 ± 37.8	91.6 ± 38.7	
Median (IQR)	95.7 (71.0–125.0)	105.0 (78.6–136.0)	95.4 (72.0–124.0)	87.0 (68.0–116.2)	83.0 (63.0–114.0)	
Total cholesterol (mg/dL)						
N	2067	665	757	469	176	<0.0001
Mean ± SD	169.9 ± 49.3	179.0 ± 50.0	167.0 ± 50.1	165.9 ± 46.0	159.2 ± 46.8	
Median (IQR)	163.0 (134.0–199.7)	173.3 (144.0–211.0)	160.0 (133.0–194.0)	161.0 (133.0–191.0)	148.0 (124.8–189.0)	
Atrial fibrillation	180/2371 (7.6%)	42/747 (5.6%)	46/904 (5.1%)	79/523 (15.1%)	13/197 (6.6%)	<0.0001
LV ejection fraction (%)						
N	1608	622	538	382	66	<0.0001
Mean ± SD	52.5 ± 11.3	50.8 ± 10.6	52.7 ± 11.1	54.3 ± 12.3	54.6 ± 11.6	
Median (IQR)	55.0 (46.0–60.0)	51.0 (45.0–60.0)	55.0 (48.0–60.0)	57.0 (50.0–62.0)	60.0 (50.0–60.0)	

SD, standard deviation; IQR, interquartile range; LDL, low-density lipoprotein; LV, left ventricle.

was reported in 24.5 and 20.2% of the cases, respectively, but a history of STEMI and NSTEMI was less common in the PAD cohort (10.9 and 6.5%, respectively).

About 67.5% of the patients had a previous history of stable CAD, and most of these patients were in Canadian Cardiovascular Society, Class I or II (71.9%). A history of previous stable CAD was less frequent in the ACS PCI and PAD cohorts. About 46.4% of the patients had undergone a previous PCI and 14.7% a previous coronary artery bypass surgery, and the proportion of patients with a previous peripheral revascularization was much higher in the PAD patients (33.3%) than in the other cohorts (3.2–3.7%).

Approximately 16.4% had experienced a previous cerebrovascular disease and 15.1% had a history of atrial fibrillation. Chronic obstructive pulmonary disease was reported in 7.0% of the patients and malignancy in 6.6%. About 54.8% of the patients had at least three of the following major cardiovascular risk factors: diabetes mellitus, hypertension, hypercholesterolaemia, smoking, or early manifestation of cardiovascular disease, and the proportion was particularly high (70.6%) in PAD patients.

Previous cerebrovascular disease was reported in 44.3% of the PAD patients, compared with 11–17.1% in the other cohorts. Similarly, a history of chronic kidney disease was more common in the PAD cohort (16.5 vs. 9.3–13.6%).

Investigations

Non-invasive investigations

Baseline investigations performed during admission/consultation or during the previous year are given in *Table 2*. Mean serum creatinine was slightly increased in this elderly population as was fasting glucose. Fasting glucose was higher in the PAD and ACS PCI cohorts than in the other two cohorts.

Total cholesterol was 169.9 ± 49.3 mg/dL and low-density lipoprotein (LDL) cholesterol was 101.7 ± 42.7 mg/dL. LDL cholesterol was higher in the ACS PCI patients than that in the other patients.

An echocardiogram was performed in 69.5% of the patients with important variations between cohorts (84.0% in cohort 1 vs. 60.4% in cohort 2, 77.4% in cohort 3, and 35.8% in cohort 4). When measured, mean ejection fraction was in the normal range

Table 3 Drug treatment before hospital admission/consultation

	Cohort, all	Cohort 1, ACS PCI	Cohort 2, elective PCI	Cohort 3, stable CAD	Cohort 4, PAD	*P*-value
No. of patients	2420	755	933	531	201	
ACE-Is	1163/2312 (50.3%)	313/711 (44.0%)	518/899 (57.6%)	257/515 (49.9%)	75/187 (40.1%)	<0.0001
ARBs	424/2333 (18.2%)	98/724 (13.5%)	188/903 (20.8%)	83/519 (16.0%)	55/187 (29.4%)	<0.0001
ACE-I/ARBs	1568/2311 (67.8%)	408/711 (57.4%)	696/898 (77.5%)	336/515 (65.2%)	128/187 (68.4%)	<0.0001
Beta-blockers	1489/2333 (63.8%)	392/722 (54.3%)	662/907 (73.0%)	347/516 (67.2%)	88/188 (46.8%)	<0.0001
MRAs	177/2341 (7.6%)	36/728 (4.9%)	70/909 (7.7%)	58/517 (11.2%)	13/187 (7.0%)	0.0007
Diuretics	717/2334 (30.7%)	171/725 (23.6%)	280/910 (30.8%)	183/513 (35.7%)	83/186 (44.6%)	<0.0001
DHP calcium channel blockers	462/2355 (19.6%)	114/735 (15.5%)	199/915 (21.7%)	92/518 (17.8%)	57/187 (30.5%)	<0.0001
Non-DHP calcium channel blockers	47/2370 (2.0%)	15/737 (2.0%)	17/923 (1.8%)	11/522 (2.1%)	4/188 (2.1%)	0.9828
Amiodarone	66/2366 (2.8%)	16/737 (2.2%)	19/922 (2.1%)	19/518 (3.7%)	12/189 (6.3%)	0.0043
Statins	1551/2298 (67.5%)	347/706 (49.2%)	716/900 (79.6%)	342/508 (67.3%)	146/184 (79.3%)	<0.0001
Nitrates	262/2357 (11.1%)	75/736 (10.2%)	133/914 (14.6%)	43/519 (8.3%)	11/188 (5.9%)	0.0001
Ivabradine	73/2365 (3.1%)	14/737 (1.9%)	40/918 (4.4%)	19/522 (3.6%)	–	0.0019
Ranolazine	32/2366 (1.4%)	7/738 (0.9%)	17/921 (1.8%)	6/519 (1.2%)	2/188 (1.1%)	0.4153
Insulin	215/2296 (9.4%)	73/694 (10.5%)	55/893 (6.2%)	46/523 (8.8%)	41/186 (22.0%)	<0.0001
Oral antidiabetics	472/2377 (19.9%)	128/739 (17.3%)	198/924 (21.4%)	98/524 (18.7%)	48/190 (25.3%)	0.0393
Oral anticoagulant drugs	215/2352 (9.1%)	39/729 (5.3%)	77/914 (8.4%)	72/521 (13.8%)	27/188 (14.4%)	<0.0001
ASA	1594/2337 (68.2%)	376/721 (52.1%)	727/913 (79.6%)	340/517 (65.8%)	151/186 (81.2%)	<0.0001
Clopidogrel	697/2352 (29.6%)	161/729 (22.1%)	382/911 (41.9%)	81/523 (15.5%)	73/189 (38.6%)	<0.0001
Other antiplatelet agents excluding clopidogrel	79/2352 (3.4%)	22/729 (3.0%)	39/911 (4.3%)	13/523 (2.5%)	5/189 (2.6%)	0.2434

χ^2 or Fisher's exact test [a] is used for binary variables.
ACE-I, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; MRAs, mineralocorticoid receptor antagonists; DHP, dihydropyridine; ASA, acetylsalicylic acid.

(52.5 ± 11.3%), whereas left ventricular hypertrophy was reported in nearly half of the patients.

A Holter monitoring was performed in 14.5% of the patients, mainly in cohorts 1 and 3 (13.7 and 28.0%, respectively).

An exercise test was performed during/within 1 year preceding admission/consultation in 21.2% of the cases, whereas stress imaging techniques were uncommon [myocardial scintigraphy 4.0%, cardiac computed tomography (CT) 2.0%, and cardiac magnetic resonance imaging (MRI) 0.9%]. An implantable cardioverter defibrillator had been implanted in only 2.2% of the patients before admission.

Invasive investigations

As expected, time to coronary angiography differed substantially between ACS PCI and elective PCI cohorts; 80.5% of the patients with elective angiography had their procedure done at least 1 month after the onset of symptoms, whereas 70% of the patients with NSTEMI were referred to the catheter laboratory within 72 h.

About 15.6% of the patients enrolled in cohorts 1 and 2 had left main disease and 33.5% a single vessel (>50%) disease, whereas 27.9% had lesions on two arteries and 22.9% on three arteries.

Fractional flow reserve (3.7%), thrombus aspiration (1.5%), and optical CT (0.8%) concerned only a limited number of patients.

Drug treatments

Table 3 provides the drug treatments before admission/consultation and *Table 4* treatments at discharge. Before admission, angiotensin-converting enzyme-inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) were prescribed in 67.8%, beta-blockers in 63.8%, diuretic agents in 30.7%, dihydropiridine (DHP) calcium channel blockers in 19.6%, nitrates in 11.1%, amiodarone in 2.8%, ivabradine in 3.1%, ranolazine in 1.4%, and trimetazidine in 3.8%.

Statins were prescribed in 67.5% of the patients. Atorvastatin accounted for 64.2% of those prescriptions and simvastatin 19.7% (data not shown).

Insulin therapy and oral antidiabetic agents were prescribed in 9.4 and 19.9% of the patients, respectively.

Vitamin K antagonists were prescribed in 7.4%, new oral anticoagulants in 1.8%, aspirin in 68.2%, clopidogrel in 29.6%, and other antiplatelet agents in 3.4% of the patients.

Drug treatment before admission differed between groups: patients with PAD or cerebrovascular disease were less prone to receive ACE-inhibitors or beta-blockers and more likely to be treated with dihydropyridine calcium channel blockers, statins, glucose-lowering medications, aspirin, and clopidogrel.

ACS PCI patients were less likely to be treated with ACE-Is, mineralocorticoid receptor antagonists (MRAs), diuretics, dihydropyridine calcium channel blockers, and statins before admission than the elective PCI and the stable CAD patients.

At discharge, the prescription rate of ACE-inhibitors/ARBs (82.9%), beta-blockers (80.2%), and statins (92.7%) as well as aspirin (90.3%) and clopidogrel (66.8%), or other antiplatelet agents (12.3%) markedly increased. Yet, the drug regimen at discharge

Table 4 Drug treatment at discharge/after consultation

	Cohort, all	Cohort 1, ACS PCI	Cohort 2, elective PCI	Cohort 3, stable CAD	Cohort 4, PAD	*P*-value
No. of patients	2420	755	933	531	201	
ACE-I	1573/2417 (65.1%)	565/754 (74.9%)	608/933 (65.2%)	315/529 (59.5%)	85/201 (42.3%)	<0.0001
ARBs	447/2417 (18.5%)	86/754 (11.4%)	193/933 (20.7%)	106/529 (20.0%)	62/201 (30.8%)	<0.0001
ACE-Is/ARBs	2002/2417 (82.8%)	648/754 (85.9%)	794/933 (85.1%)	415/529 (78.4%)	145/201 (72.1%)	<0.0001
Beta-blockers	1939/2417 (80.2%)	639/754 (84.7%)	758/933 (81.2%)	440/529 (83.2%)	102/201 (50.7%)	<0.0001
MRAs	276/2417 (11.4%)	99/754 (13.1%)	71/933 (7.6%)	91/529 (17.2%)	15/201 (7.5%)	<0.0001
Diuretics	876/2417 (36.2%)	222/754 (29.4%)	324/933 (34.7%)	237/529 (44.8%)	93/201 (46.3%)	<0.0001
DHP calcium channel blockers	540/2417 (22.3%)	140/754 (18.6%)	223/933 (23.9%)	113/529 (21.4%)	64/201 (31.8%)	0.0004
Non-DHP calcium channel blockers	50/2417 (2.1%)	16/754 (2.1%)	16/933 (1.7%)	13/529 (2.5%)	5/201 (2.5%)	0.7636
Amiodarone	82/2416 (3.4%)	19/753 (2.5%)	25/933 (2.7%)	27/529 (5.1%)	11/201 (5.5%)	0.0144
Statins	2241/2417 (92.7%)	717/754 (95.1%)	891/933 (95.5%)	453/529 (85.6%)	180/201 (89.6%)	<0.0001
Nitrates	293/2417 (12.1%)	109/754 (14.5%)	94/933 (10.1%)	75/529 (14.2%)	15/201 (7.5%)	0.0033
Ivabradine	99/2417 (4.1%)	23/754 (3.1%)	52/933 (5.6%)	22/529 (4.2%)	2/201 (1.0%)	0.0067
Ranolazine	33/2417 (1.4%)	7/754 (0.9%)	16/933 (1.7%)	8/529 (1.5%)	2/201 (1.0%)	0.5310
Insulin	238/2337 (10.2%)	84/711 (11.8%)	59/899 (6.6%)	47/526 (8.9%)	48/201 (23.9%)	<0.0001
Oral antidiabetics	485/2417 (20.1%)	139/754 (18.4%)	197/933 (21.1%)	96/529 (18.1%)	53/201 (26.4%)	0.0444
Oral anticoagulant drugs	275/2415 (11.4%)	63/754 (8.4%)	87/932 (9.3%)	94/528 (17.8%)	31/201 (15.4%)	<0.0001
ASA	2183/2417 (90.3%)	700/754 (92.8%)	887/933 (95.1%)	416/529 (78.6%)	180/201 (89.6%)	<0.0001
Clopidogrel	1615/2417 (66.8%)	518/754 (68.7%)	795/933 (85.2%)	126/529 (23.8%)	176/201 (87.6%)	<0.0001
Other antiplatelet agents excluding clopidogrel	298/2417 (12.3%)	199/754 (26.4%)	75/933 (8.0%)	20/529 (3.8%)	4/201 (2.0%)	<0.0001

χ^2 or Fisher's exact test [a] is used for binary variables.
ACE-I, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; MRAs, mineralocorticoid receptor antagonists; DHP, dihydropyridine; ASA, acetylsalicylic acid.

differed between the four cohorts, particularly between PAD patients and those included in the other three cohorts.

This was also true for combination therapy: 71.5% of the patients received a combination of ACE-I/ARB, aspirin, and statins at discharge when compared with only 44.5% before admission.

The rate of prescription of recent antianginal agents was low, 4.1% for ivabradine and 1.4% for ranolazine, as was the utilization of new antiplatelet agents except in cohort 1 (26.4%).

Table 5 summarizes key demographic data and management modalities in the current CICD-Pilot registry and in the previous Euro Heart Survey (EHS) on stable angina published in 2005.

Only three patients died in hospital: one in cohort 1, one in cohort 3, and one in cohort 4.

Discussion

The CICD-Pilot survey shows substantial trends in the changing profile of patients with CICD in Europe as well as management modalities. It also shows important differences across the four cohorts of patients.

Clinical profile

Compared with a previous EHS conducted in Europe and including 3779 patients with stable angina pectoris, patients enrolled in the CICD-Pilot survey were older and had more frequently a history of diabetes, dyslipidaemia, hypertension, cerebrovascular disease, and malignancy, whereas the rate of chronic pulmonary disease was similar.[6] Also the proportion of patients with severe angina defined by a CCS class III was higher in the cohort of patients with planned PCI than in the previous survey. These findings suggest that patients with CICD are more complex and have more comorbidities than 10 years ago.

The plasma level of LDL cholesterol was lower in our registry than that in the previous EHS. This likely reflects a higher prescription rate of statins (67 vs. 48%) and other lipid-lowering agents and suggests that guideline recommendations for the management of hypercholesterolaemia are better implemented. The mean LDL plasma level reported here remains, however, higher than the current recommended target in patients with established cardiovascular disease (≤70 mg/dL).[4]

The clinical profile of the patients enrolled in the CICD registry is closer to that of patients enrolled in the CLARIFY registry, a large contemporary international registry of patients with stable CAD with/without angina and with/without documented ischaemia enrolled in many countries across the world.[8]

We also observed important differences in the clinical profile of the four cohorts of patients. Specifically, PAD patients were older, had a higher systolic blood pressure, were more likely to be males, smokers, or to be affected by comorbidities such as diabetes mellitus, hypertension, chronic kidney disease, cerebrovascular disease, or chronic obstructive pulmonary disease than the other patients. This finding illustrates the broad spectrum of clinical presentation of patients affected by atherosclerosis and confirms data from large international registries.[7]

Table 5 Comparison of patients enrolled in the CICD-Pilot registry (2015) and in the EHS (2005[6])

	CICD-Pilot (2015)	EHS (2005)
No. of patients	2420	3779
Age (mean ± SD)	66.6 ± 10.9	61 ± 11
% Male	69.5	58
Medical history		
Diabetes mellitus (%)	29.2	18
Dyslipidaemia (%)	74.1	58
Hypertension (%)	82.6	62
Previous cerebrovascular disease (%)	16.4	5
Malignancy (%)	6.6	2
Investigations		
Echocardiography (%)	70	64
Ischaemia stress tests (%)[a]	50 (stable CAD)/ 37 (elective PCI)	76/18
Treatment at discharge		
ACE-I	65.1	40
Beta-blockers	80.2	67
Statins	92.7	48
Aspirin	90.3	78
Nitrates	11.1	61
Calcium channel blockers	24	27

CICD, chronic ischaemic cardiovascular disease; EHS, Euro Heart Survey; SD, standard deviation; CAD, coronary artery disease; PCI, percutaneous coronary intervention; ACE-I, angiotensin-converting enzyme inhibitor; MRI, magnetic resonance imaging.
[a]CICD: before/during hospitalization. EHS: during hospitalization/planned. Exercise test (76)/stress imaging (18).

Investigations

Evaluation of cardiac function by echocardiography is recommended by the ESC guidelines in all patients with stable CAD in order to identify regional wall motion abnormalities, measure ejection fraction, and evaluate diastolic function.[3] In the CICD-Pilot registry, it was measured only in ~70% of the patients overall and only in one-third of patients with PAD.

Assessment of myocardial ischaemia during hospitalization/consultation or within 1 year was made in only 50% of the patients with stable CAD and 37% of those with planned elective angioplasty, a much smaller proportion than that observed in the previous European survey.

The use of new imaging modalities including cardiac CT, myocardial scintigraphy, or cardiac magnetic resonance was marginal, and most of the stress test procedures used conventional exercise test. The low rate of use of modern imaging modalities may in part be explained by geographic variations and related differences in access to these techniques as >40% of our patients were recruited in Central/Eastern European countries. We indeed found that there was a statistically significant lower use of stress imaging modalities (myocardial scintigraphy, $P < 0.001$ and MRI, $P < 0.0022$) and of CT scan, $P < 0.001$, in Eastern countries, compared with the other three European regions.

Nevertheless, these findings show that implementation of the recent ESC guidelines in which imaging stress testing plays a central role remains suboptimal and that there is room for improvement.

Drug treatments

Important differences exist between this pilot registry and the previous EHS regarding antianginal therapies at discharge: the use of beta-blockers was higher in the current survey, whereas nitrates were prescribed nearly five times less and calcium antagonists slightly less than in the EHS population.

Similarly, the use of ACE-inhibitors and aspirin was markedly higher in the CICD-Pilot survey. As the use of other antiplatelet agents was not recorded in EHS, no comparison is possible with our study regarding this point.

Differences inherent to the constitution of cohorts (i.e. NSTEMI and PAD patients) may account for some of the variations observed in drug therapy. We indeed observed that PAD patients were less likely to be treated by ACE-Is, beta-blockers, MRAs, or antianginal drugs and more likely to be on diuretic agents, dihydropyridine calcium channel blockers, insulin, or oral antidiabetic agents than the patients enrolled in the other cohorts. In contrast, use of aspirin at discharge was high (except in stable CAD patients) as was the use of clopidogrel or other antiplatelet agents. Overall, our findings suggest that guideline-recommended therapies are better implemented in the current registry than they were in 2005.

Another important observation is the fact that both antianginal drugs and drugs recommended for secondary prevention were substantially more prescribed at discharge than before admission or consultation, suggesting that physicians taking care of the patients enrolled in the CICD-Pilot registry tried to implement guideline-recommended therapies.[4]

Overall, the rate of prescription of therapies used in secondary prevention is similar to that observed in the most recent EuroAspire IV studies.[9,10] In these large European registries enrolling patients from 78 centres in 24 countries with established CAD, a high use of these therapies was reported, but large variations in secondary prevention practice were noticed among centres.

There are, however, important differences in the rate of prescription of life-saving drugs or antianginal medications between the CICD-Pilot survey and the CLARIFY registry: the rate of prescription of ACE-Is/ARBs, beta-blockers, aspirin, and particularly of thienopyridines at discharge is higher in the CICD-Pilot registry. This is partly due to the fact that our study enrolled patients with NSTEMI, but geographic variations between different regions of the world may also be responsible for these differences.

This registry has important limitations.

Although the setting of recruiting centres was clearly defined and uniform across different countries (catheter laboratory for cohorts 1, 2, and 4 and clinics in hospital without cardiovascular interventional facilities for cohort 3), selection of centres was made on a voluntary basis, and we therefore cannot exclude a centre bias regarding the clinical profile, the investigations, and the treatment of patients enrolled.

Medical history was recorded by investigator's report as usually performed in observational studies. However, guidance was provided in the case report form for important definitions including hypertension, hyperlipidaemia, or myocardial infarction.

Important heterogeneity also exists between the cohorts due to different inclusion criteria, but the registry has tried to capture all aspects of CICD, except STEMI and recent stroke.

Important geographic variations may also exist and reflect different levels of availability/affordability of diagnostic procedures and treatments. The limited size of the current pilot registry makes analysis of these potential geographic variations difficult and could lead to erroneous conclusions. It should be better evaluated in the forthcoming European long-term registry.

As we did not record the dosage of main classes of anti-ischaemic or preventive medications, we are unable to assess the proportion of patients at target recommended doses.

Finally, this registry being a pilot phase, only a limited number of countries are represented. Nevertheless, this registry demonstrated the feasibility of this data collection on CICD in 10 European countries and will be followed by a long-term registry, including all volunteer members of the ESC with outcome measures.

In summary, the CICD-Pilot registry enrolled patients with the whole spectrum of ischaemic cardiovascular artery disease, except for patients with ST elevation ACS.

It shows that European patients with CICD tend to have multiple comorbidities and that diagnostic procedures recommended by international guidelines are not put in practice in all patients. There is, however, a trend for better treatment by antianginal medications and preventive drugs, compared with previous observations. Whether this improvement in the management of CICD impacts favourably on outcomes deserves follow-up studies such as the forthcoming long-term CICD registry of the ESC.[9,10]

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Appendix

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