Cohort profile

The ESC-EORP Chronic Ischemic Cardiovascular Disease Long-Term (CICD LT) registry

Michel Komajda[1], Francesco Cosentino[2], Roberto Ferrari[3,7], Cécile Laroche[4], Aldo Maggioni[4,5], Philippe Gabriel Steg[6], Luigi Tavazzi[7], Mathieu Kerneis[8], Marco Valgimigli[9], Chris P. Gale[10],

on behalf of the CICD investigators group*

*A complete list of the CICD Investigators is provided in the appendix 1

Affiliations

[1] Department of cardiology, Saint Joseph Hospital, Paris, France

[2] Unit of Cardiology, Karolinska Institutet and Karolinska University Hospital Solna, Stockholm, Sweden

[3] Centro Cardiologico Universitario di Ferrara, University of Ferrara, Ferrara, Italy

[4] EURObservational Research Programme, European Society of Cardiology, Sophia-Antipolis, France

[5] ANMCO Research Center, Florence, Italy

[6] Hôpital Bichat, Assistance Publique-Hôpitaux de Paris and Université de Paris, Paris, France

[7] Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy

[8] Sorbonne Université, ACTION Study Group, INSERM UMRS1166, ICAN - Institute of CardioMetabolism and Nutrition Institut de Cardiologie, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France.

[9] Bern University Hospital, Inselspital, Bern, Switzerland

[10] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds; Leeds Institute for Data Analytics, University of Leeds; Department of Cardiology, Leeds Teaching Hospitals NHS Trust, United Kingdom

Corresponding Author:

Prof Michel Komajda

Department of cardiology

Saint Joseph Hospital

Paris France

michel.komajda@noos.fr

Phone 33661744848

Mail mkomajda@hpsj.fr

Abstract

Aims: The European Society of cardiology (ESC) EURObservational Research Programme (EORP) Chronic Ischemic Cardiovascular Disease registry Long Term (CICD) aims to study the clinical profile, treatment modalities and outcomes of patients diagnosed with CICD in a contemporary environment in order to assess whether these patients at high cardiovascular risk are treated according to ESC guidelines on prevention or on stable coronary disease and to determine mid and long term outcomes and their determinants in this population

Methods and results: 9174 patients over 18 years with documented CICD defined by an history acute coronary syndrome with /without ST elevation ,previous coronary revascularization or stable coronary artery disease were enrolled between May 1st 2015 and July 31st 2018.Individual patient data on clinical profile, biology and treatment modalities were collected across 154 centers from 20 ESC countries.

A two years follow up is scheduled in order to determine the following clinical outcomes: all cause and cardio-vascular (CV) death, all cause and cardio-vascular hospitalizations, changes in medications and quality of life using the EuroQol5D-5L score.

Conclusion: The CICD Long Term is an international registry of care and outcomes of patients hospitalised with Chronic Ischemic Cardiovascular Disease which will provide insights into the contemporary profile and management of patients with this common disease.

Key words:

Chronic Coronary Disease, registry, clinical outcomes, demographics, medications

Introduction

Chronic ischemic coronary disease is a major burden on public health and affects millions of patients worldwide. It is also one of the major causes of death in Europe (1-4)

Over the years, the clinical characteristics, risk factors, treatment modalities and clinical outcomes have changed markedly due to new imaging modalities, improved prevention awareness and more efficient revascularization therapies whereas ageing populations are more prone to develop this condition.

Moreover, important geographic disparities in presentation, diagnostic procedures treatment modalities and clinical outcomes have been identified. (5,6)

In this context, it is important to reassess in a contemporary environment the clinical profile, diagnostic modalities, treatment and clinical outcomes of a large ESC population affected by chronic ischemic coronary disease and to identify potential geographic variations as well as determinants of major clinical events.

We therefore designed and implemented the ESC EORP Chronic ischemic cardio vascular disease (CICD) registry to undertake a contemporary investigation of the profile, care and outcomes across ESC countries based on the experience acquired from the CICD pilot registry(7,8).The population enrolled in the CICD registry Long term is intended to reflect the entire spectrum of patients with CICD in the heterogeneous context of the ESC countries and our data will be compared to those from other international registries

Aim of CICD:

The ESC EORP CICD Long term registry is an international prospective observational longitudinal registry. The aims of the CICD registry are:

To characterize CICD patients in terms of:

- demographic characteristics
- clinical profiles

- management according to the clinical profiles and potential gaps between routine treatments and evidenced-based therapies recommended by ESC guidelines on the management of stable coronary artery disease published in 2013 and guidelines on cardiovascular disease prevention published in 2016

To determine mid and long term (1 and 2 years) outcomes and their determinants.

Selection and invitation of Centres

University and non-university hospitals of any volume of activity within ESC countries were invited to join CICD on a voluntary basis. All 57 ESC member countries were invited to participate in CICD, with centres within the countries being selected by a National Coordinator from the country.

In each participating country, the total number of centres was selected on the basis of the number of inhabitants by country:

- 2 centres every 1 million inhabitants for countries with a population inferior to 5 million inhabitants,
- 1 centre every million from 5 to 30 million inhabitants and
- At least 1 centre every 2 million inhabitants for countries with a population superior to 30 million inhabitants.

The total number of centres in each participating country was split according to the proportion of existing centres with/without a catheterization laboratory facility.

Centres with catheter laboratory facilities enrolled patients who were or were not revascularized.

The investigator centres were accepted on a voluntary basis through national coordinators, according to the criteria reported above.

Each National Coordinator supplied to the Executive Committee a list of potential medical/surgical centres technically suitable to set up such a registry and was requested to indicate whether the proposed medical centre was a referral/community, with/without cardiac surgery, with/without interventional cardiology

As far as possible, we tried to propose centres that were evenly distributed across geographical areas within each country.

The site characteristics are described on the CICD specific Case Report Form (CRF).

By means of an electronic case record form, individual patient data were collected across 230 variables (583 including the dependent questions). These data include patient characteristics, clinical, biological, and treatment modalities. Follow-up data will include the major clinical outcomes listed above

The CICD LT registry is managed by the ESC EurObservational team under the control of an executive committee (composition see annex) made of experts in the management of chronic ischemic cardiovascular diseases.

Population and consent

9174 patients were enrolled in 154 centers from 20 ESC countries, All consecutive patients aged over 18 years with a CICD diagnosis included had either a routine follow up after an acute coronary syndrome (both ST and non ST elevation acute coronary syndrome) or elective revascularization or had an established stable coronary disease .

Established stable coronary artery disease was defined as effort induced angina or rest angina with documented myocardial ischemia detected by exercise test or any stress imaging or presence of a documented >50% stenosis in a least one major coronary artery.

Patients presenting with an acute coronary syndrome in the previous 30 days were excluded.

All participants received detailed written information concerning the study and provided signed informed consent

Patient identification: Participants were identified according to CICD inclusion criteria and were given a unique study number.

Inclusion criteria have been defined as:

- Patient has signed the informed consent for the primary objectives
- Patient has signed the informed consent for the secondary objectives
- Patient age 18 years or above
- -Presenting with CICD as defined above

Start points: Any patient aged over 18 years and hospitalised between May 1st, 2015 to July 31st, 2018 with CICD as defined above. Consecutive recruitment was requested in each participating center.

Baseline and follow-up data:

Baseline data included demographic data(site of inclusion, type of site, type of CICD inclusion sub-category, age, sex), medical history including risk factors, co-morbidities, clinical data, previous cardiac revascularization and type of revascularization, electrocardiographic data, echocardiographic ejection fraction, classes of medications before inclusion and after the admission/outpatient inclusion visit, detailed standard biology, C reactive protein.

Follow up data include death and cause of death (cardiovascular/non cardio-vascular), rehospitalizations (all cause and cardiovascular) medications (rates of prescriptions) and quality of life data using the EuroQol5D-5L scoring system.

Follow up is scheduled at one year (closed Q4 2019) and two years (closed Q4 2020)

Data capture and storage: Participant identifiable data were used to track subsequent clinical care and outcomes, with the identifiable data only residing on local centre computers. These data were then pseudonymised by means of a unique patient study code before electronic transmission via the ESC-EORP Data Entry System Security using SSL (Secure Sockets Layer) network encryption to a dedicated secure server (Microsoft SQL Server 2012 Database server) at the central data warehouse (The European Heart House, France). Data Collection Officers and local investigators at participating centres had access to electronic case report forms through secure login on the EORP website. Individual login names and passwords were distributed by the EORP team to the participating centres.

Data quality Data quality was monitored by the ESC EORP CICD administrative and data management team. This included edit checks (for missing data, date chronology, numeric value ranges) and a Data Validation Plan listing all the checks carried out to ensure data consistency and adherence to the protocol, including missing data, consistency of the chronology in the dates and between the data of the different visits of the study (cross checks), and the numeric values entered are included in the predefined ranges

Endpoints and linkage to other data:

The primary end point is the composite of cardio vascular death or cardio vascular rehospitalisation at one and two years and secondary endpoints include all cause death or all cause rehospitalization, cardio vascular death, cardiovascular rehospitalisation, all cause re-hospitalisation rate of prescription of recommended therapies quality of life assessed by the EuroQol 5D scoring system. Data will be collected from participating centers medical records, contacts with physicians and if needed contact with participants by telephone.

Conclusion:

The ESC EORP CICD registry is a comprehensive and far reaching observational cohort of patients with CICD. The registry will describe the contemporary profile of patients admitted to both general and referral hospitals with CICD, their investigations, treatment and clinical outcomes in 20 ESC countries and document how we care for patients with CICD in the light of recommendations from the 2013 ESC Clinical Practice Guidelines for the management of stable coronary disease (to be updated in 2019) and from the 2016 prevention guidelines . CICD will, in particular indicate whether this high cardiovascular risk population is treated by recommended preventive classes of medications and if geographic variations are observed across participating countries. CICD LT data will be compared to data deriving from other international registries

Acknowledgements

EORP Oversight Committee, Registry Executive and Steering Committees. Data collection was conducted by the EORP department of the ESC: Souad Mekhaldi as Clinical Project Manager, Patti-Ann McNeill as Project Officer, Viviane Missiamenou as Data Manager, Statistical analyses were performed by Cécile Laroche. Scientific activities were coordinated and supervised by Doctor Aldo P. Maggioni, EORP Scientific Coordinator.

Funding

Since the start of EORP, the following companies have supported the programme: Abbott Vascular Int. (2011-2021), Amgen Cardiovascular (2009-2018), AstraZeneca (2014-2021), Bayer (2009-2018), Boehringer Ingelheim (2009-2019), Boston Scientific (2009-2012), The Bristol Myers Squibb and Pfizer Alliance (2011-2016), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2011-2017), Edwards (2016-2019), Gedeon Richter Plc. (2014-2017), Menarini Int. Op. (2009-2012), MSD-Merck & Co. (2011-2014), Novartis Pharma AG (2014-2020), ResMed (2014-2016), Sanofi (2009-2011), SERVIER (2010-2021), Vifor (2019-2022).

Conflict of Interest statement

Dr. Cosentino reports personal fees from Novo Nordisk, personal fees from MSD, personal fees from Pfizer, personal fees from Mundipharma, personal fees from Eli Lilly, personal fees from BI, personal fees from AstraZeneca, personal fees from BMS, outside the submitted work;

Dr. Ferrari reports grants and personal fees from SERVIER INTERNATIONAL, personal fees from MERCK SERONO, personal fees from BAYER, grants and personal fees from NOVARTIS, personal fees from BOEHRINGER INGELHEIM, personal fees from

ALFASIGMA, personal fees from PFIZER, personal fees from CIPLA, outside the submitted work;

Prof. Gale reports non-financial support from Bayer, grants, personal fees and non-financial support from Bristol Myers Squib, personal fees and non-financial support from Novartis, personal fees and non-financial support from AstraZeneca, personal fees from Vifor Pharma, grants from Abbot, personal fees from Daiichi sankyo, outside the submitted work;

Dr. Kerneis reports grants from Institut Servier, grants from Federation Francaise de Cardiologie, personal fees from Servier, personal fees from Sanofi, personal fees from Bayer, outside the submitted work;

Prof Komajda reports personal fees from NOVARTIS, SERVIER, MSD, SANOFI, ASTRA ZENECA, TORRENT, outside the submitted work;

Mrs Laroche has nothing to disclose.

Dr. Maggioni reports personal fees from Bayer, personal fees from Fresenius, personal fees from Novartis, outside the submitted work;

Dr. Steg reports grants and personal fees from Bayer/Janssen, grants and personal fees from Merck, grants and personal fees from Sanofi, grants and personal fees from Amarin, personal fees from Amgen, personal fees from Bristol Myers Squibb, personal fees from Boehringer-Ingelheim, personal fees from Pfizer, personal fees from Novartis, personal fees from Regeneron, personal fees from Lilly, personal fees from AstraZeneca, grants and personal fees from Servier, outside the submitted work;

Dr. Tavazzi reports personal fees from SERVIER, personal fees from CVIE Therapeutics, outside the submitted work

Dr. Valgimigli reports personal fees from Astra Zeneca, grants and personal fees from Terumo, personal fees from Alvimedica/CID, personal fees from Abbott Vascular, personal fees from Daiichi Sankyo, personal fees from Opsens, personal fees from Bayer, personal fees from

CoreFLOW, personal fees from IDORSIA PHARMACEUTICALS LTD, personal fees from Universität Basel | Dept. Klinische Forschung, personal fees from Vifor, personal fees from Bristol Myers Squib SA, personal fees from iVascular, personal fees from Medscape, outside the submitted work

References:

1. Leal J, Luengo-Fernández R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. *European heart journal.* Jul 2006;27(13):1610-1619.

2. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet.* May 8 1999;353(9164):1547-1557.

3. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet.* May 24 1997;349(9064):1498-1504.
Daly CA, Clemens F, Sendón JL, Tavazzi L, Boersma E, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM. The clinical characteristics and investigations planned in patients with stable angina presenting to cardiologists in Europe: from the Euro Heart Survey of Stable Angina. *European heart journal.* May 2005;26(10):996-1010.

4. Daly CA, Clemens F, Sendón JL, Tavazzi L, Boersma E, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM. The clinical characteristics and investigations planned in patients with stable angina presenting to cardiologists in Europe: from the Euro Heart Survey of Stable Angina. *European heart journal.* May 2005;26(10):996-1010.

5. Steg PG, Bhatt DL, Wilson PW, D'Agostino R, Sr., Ohman EM, Rother J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S. One-year cardiovascular event rates in outpatients with atherothrombosis. *Jama.* Mar 21 2007;297(11):1197-1206.

6. Steg PG, GreenlawN, Tendera M et al

Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease:data from the international Observational CLARIFY Registry.JAMAIntern Med 2014;174:1651-1659

7. Komajda M,Weidinger F, kerneis M . et al

Euroobservational Research Programme:the Chronic Ischaemic CardioVascular Disease Registry:pilot phase (CICD-Pilot)Eur heart J 2016;37:152-160

8. Komajda M, Kerneis M Tavazzi L et al

The Chronic ischaemic cardiovascular disease ESc pilot Registry : results of the six month follow up, European journal of preventive cardiology 2018;4:377-87

Figure legends:

Figure 1: Patients enrolment per country in the ESC EORP CICD registry

Table 1: Numbers of patients included in the ESC EORP CICD registry according to participating countries. Patients analysed (by country and type of visit)

Table 2: Recruitment by country and by type of inclusion criteria in the ESC EORP CICD registry

Figure 1. Patients enrolment per country in the ESC EORP CICD registry

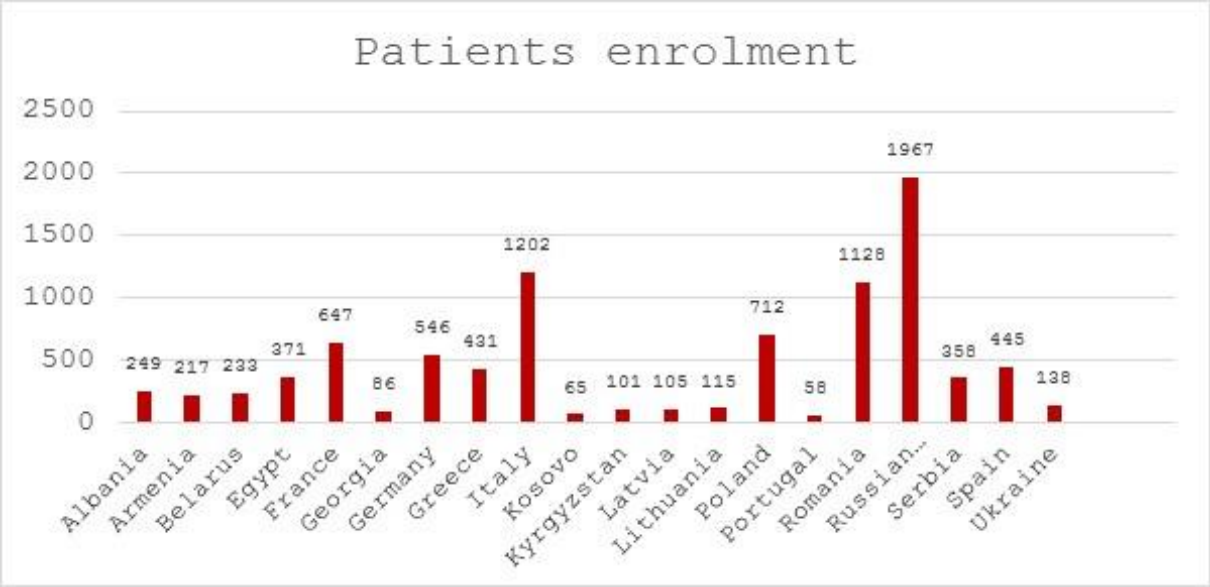

Table 1. Numbers of patients included in the ESC EORP CICD registry according to participating countries**.** Patients analysed (by country and type of visit)

Countries	**All (n =9174)**	**Routine visit (n =7061)**	**Elective revascularisation procedure (n =2113)**
ESC countries	9174	7061	2113
Albania	249	206	43
Armenia	217	216	1
Belarus	233	215	18
Egypt	371	194	177
France	647	551	96
Georgia	86	51	35
Germany	546	269	277
Greece	431	250	181
Italy	1202	804	398
Kosovo	65	50	15
Kyrgyzstan	101	100	1
Latvia	105	49	56
Lithuania	115	82	33
Poland	712	585	127
Portugal	58	5	53
Romania	1128	994	134
Russian Federation	1967	1652	315

Serbia	358	319	39
Spain	445	428	17
Ukraine	138	41	97

Table 2. Recruitment by country and by type of inclusion criteria in the ESC EORP CICD registry

Countries	All (n =9174)	Previous STEMI (n =3497)	Previous NSTE ACS (n =2177)	Previous coronary revascularisation (n =1682)	Stable coronary artery disease (n =1818)
ESC countries	9174	3497	2177	1682	1818
Albania	249	72	52	25	100
Armenia	217	82	41	13	81
Belarus	233	146	47	12	28
Egypt	371	114	55	46	156
France	647	256	152	179	60
Georgia	86	31	35	4	16
Germany	546	81	75	259	131
Greece	431	119	90	104	118
Italy	1202	382	409	231	180
Kosovo	65	36	9	8	12
Kyrgyzstan	101	22	33	0	46
Latvia	105	24	8	39	34
Lithuania	115	46	31	11	27
Poland	712	158	260	139	155
Portugal	58	4	7	10	37
Romania	1128	453	259	166	250
Russian Federation	1967	1029	365	284	289
Serbia	358	178	81	69	30
Spain	445	202	154	67	22

Ukraine	138	62	14	16	46

STEMI= ST segment elevation myocardial infarction; NSTE ACS= Non–ST-Elevation Acute Coronary Syndrome.

Table 1. Numbers of patients included in the ESC EORP CICD registry according to participating countries**.** Patients analysed (by country and type of visit)

Countries	**All (n =9174)**	**Routine visit (n =7061)**	**Elective revascularisation procedure (n =2113)**
ESC countries	9174	7061	2113
Albania	249	206	43
Armenia	217	216	1
Belarus	233	215	18
Egypt	371	194	177
France	647	551	96
Georgia	86	51	35
Germany	546	269	277
Greece	431	250	181
Italy	1202	804	398
Kosovo	65	50	15
Kyrgyzstan	101	100	1
Latvia	105	49	56
Lithuania	115	82	33
Poland	712	585	127
Portugal	58	5	53
Romania	1128	994	134
Russian Federation	1967	1652	315

Serbia	358	319	39
Spain	445	428	17
Ukraine	138	41	97

Table 2. Recruitment by country and by type of inclusion criteria in the ESC EORP CICD registry

Countries	All (n =9174)	Previous STEMI (n =3497)	Previous NSTE ACS (n =2177)	Previous coronary revascularisation (n =1682)	Stable coronary artery disease (n =1818)
ESC countries	9174	3497	2177	1682	1818
Albania	249	72	52	25	100
Armenia	217	82	41	13	81
Belarus	233	146	47	12	28
Egypt	371	114	55	46	156
France	647	256	152	179	60
Georgia	86	31	35	4	16
Germany	546	81	75	259	131
Greece	431	119	90	104	118
Italy	1202	382	409	231	180
Kosovo	65	36	9	8	12
Kyrgyzstan	101	22	33	0	46
Latvia	105	24	8	39	34
Lithuania	115	46	31	11	27
Poland	712	158	260	139	155
Portugal	58	4	7	10	37
Romania	1128	453	259	166	250
Russian Federation	1967	1029	365	284	289
Serbia	358	178	81	69	30
Spain	445	202	154	67	22

Ukraine	138	62	14	16	46

STEMI= ST segment elevation myocardial infarction; NSTE ACS= Non–ST-Elevation Acute Coronary Syndrome.