Impact of chronic coronary syndromes on cardiovascular hospitalization and mortality: The ESC-EORP CICD-LT registry

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ABSTRACT

Background: In Europe, global data on guideline adherence, geographic variations and determinants of clinical events in Chronic coronary syndrome (CCS) patients remain suboptimal.

Design: The European Society of Cardiology (ESC) EORP CICD-LT registry is a prospective European registry, was designed to describe the profile, management and outcomes of patients with CCS across the ESC countries.

Methods: We aimed to investigate clinical events at one-year follow-up from the ESC EORP CICD-LT Registry.

Results: One-year outcomes of 6655 patients from the 9174 recruited in this European registry were analyzed. Overall, 168 patients (2.5%) died, mostly from CV causes (n= 97, 1.5%). Northern Europe had the lowest CV mortality rate, while southern Europe had the highest (0.5% vs 2.0%, p= 0.04). Women had a higher rate of CV mortality compared with men (2.0% vs 1.3%, p=0.02). During follow-up, 1606 patients (27.1%) were hospitalized at least once, predominantly for CV indications (n=1220, 20.6%). Among the population with measured LDL-cholesterol level at one-year, 1434 patients (66.5%) were above the recommended target. Age, history of atrial fibrillation, previous stroke, liver disease, chronic obstructive pulmonary disease or asthma, increased serum creatinine and impaired left ventricular function were associated with an increased risk of CV death or hospitalization.

Conclusion: In the CICD registry, the majority of patients with CCS have uncontrolled CV risk factors. The one year mortality rate is low, but these patients are frequently hospitalized for CV causes. Early identification of comorbidities may represent an opportunity for enhanced care and better outcomes.

Keywords: Chronic coronary syndromes, cohort, management, outcomes

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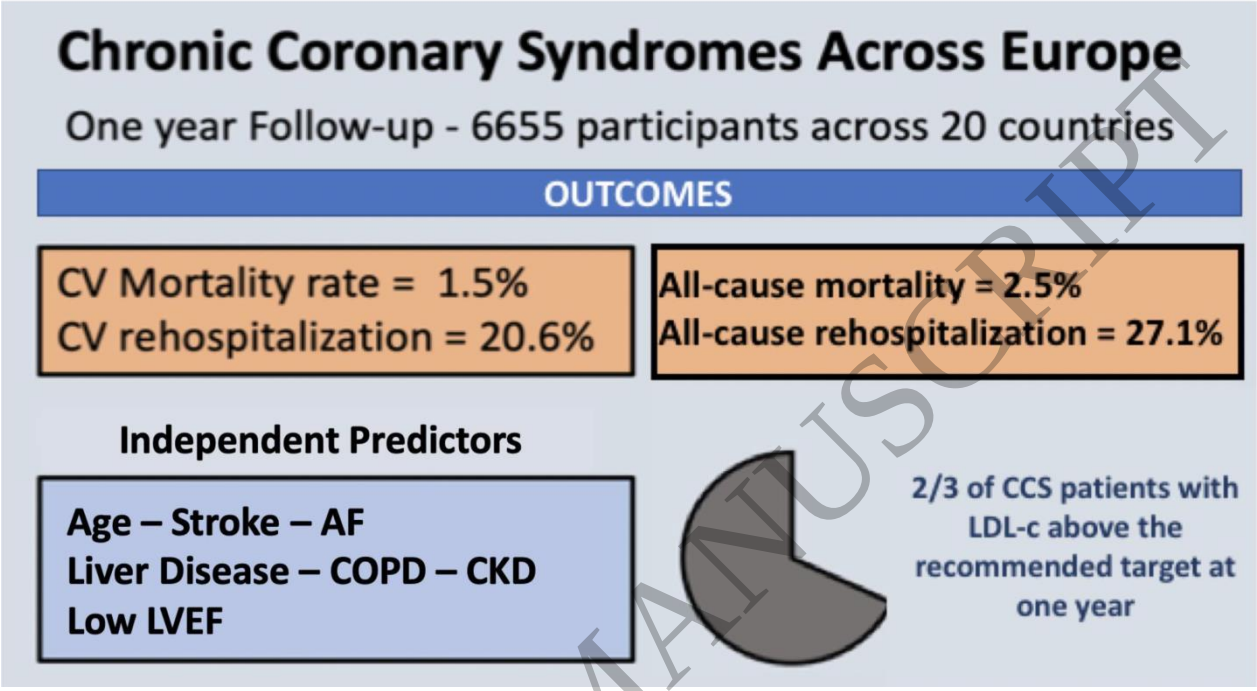

'One-sentence Summary': **:**Patients with *CCS enrolled* in the CICD registry were at high risk of rehospitalization for CV causes, suggesting that the early identification of comorbidities associated with this risk (impaired left ventricular function, atrial fibrillation, previous stroke, liver, kidney and pulmonary diseases) may represent an opportunity for enhanced care and better outcomes.

INTRODUCTION

Chronic coronary syndromes (CCS) encompass a broad spectrum of clinical scenarios resulting from atherosclerotic plaque accumulation in the coronary arteries and remain a major cause of mortality worldwide (1,2). Over the last decades, the progress in percutaneous coronary intervention techniques, pharmacology and secondary lifestyle prevention have, however, reduced the risk of major clinical outcomes for millions of patients suffering from this condition (3). Lessons from randomized trials (4) and large registries (5) have improved our understanding of the disease and identified the gap between clinical practice and international guidelines (6). In Europe, global data on guideline adherence, potential geographic variations and determinants of major clinical events in CCS remain suboptimal.

The European Society of Cardiology (ESC) EURObservational Research Programme (EORP) Chronic Ischemic Cardiovascular Disease Long-Term (CICD-LT) registry, a prospective European registry, was designed and conducted to describe the profile, care and outcomes of patients with CCS across the ESC and affiliated member countries (7,8). Pilot phase and cohort baseline data of the study found the use of guideline-recommended secondary prevention pharmacotherapy to be suboptimal (9,10). In particular, the elderly and female participants less frequently were prescribed guideline-indicated drug combinations compared with their younger and male counterparts (9). Notably, the impact of these findings on clinical outcomes is unknown.

The aim of the 1-year follow-up data of the ESC EORP CICD long term registry, was to report the patients' outcomes and identify the variables associated with an increased risk of clinical events.

METHODS

Study Population

The study design and the baseline characteristics of the population enrolled in the CICD-LT have been previously published (8,9). Briefly, the CICD-LT registry is a long-term, international, prospective, observational, longitudinal study in patients with CCS followed-up over 2 years. All ESC country members were invited to participate in the registry through National Cardiac Societies. The number of centres selected in each country was based on population size. Consecutive adults (aged ≥ 18 years) presenting with a diagnosis of CCS identified by means of a routine ambulatory visit or an elective coronary revascularization procedure at participating centres were recruited after obtaining informed consent. CCS was defined as previous myocardial infarction, previous coronary revascularization or other CCS.

The last was defined as effort-induced angina or rest angina with documented myocardial ischaemia detected by exercise or any stress imaging test or documented >50% stenosis in at least one major coronary artery on coronary angiography or asymptomatic ischaemia with a documented >50% stenosis in at least one major coronary artery on coronary angiography; Patients were excluded if they had experienced an acute coronary syndrome (ACS) in the previous 30 days.

Consecutive enrollment was facilitated through the recruitment participants at each participating centre on pre-determined days per week, up to at least 60 patients overall. The choice of the day(s) of enrollment per week was left at the discretion of the investigators and differed between centres. Baseline data collected for patients at routine ambulatory visit/elective revascularization procedure and following the hospital visit/discharge included demographic characteristics, cardiovascular risk factors, co-morbidities (history of atrial fibrillation, heart failure, stroke/ transient ischemic attack (TIA), chronic kidney disease (CKD), chronic obstructive pulmonary

disease (COPD)/asthma, liver disease, malignancy), clinical signs and symptoms and current use of pharmacological treatments. Information on clinical and survival status, obtained by phone or during out-patient visit, was collected approximately after 1 year from study inclusion. The CICD-LT registry was conducted according to the principles of the declaration of Helsinki. All patients gave written informed consent to participate, in line with national and local regulations.

Outcomes

The following outcomes were assessed at one year: all-cause death, cardiovascular (CV) and non-cardiovascular death, all causes of rehospitalization, cardiovascular, coronary artery disease (CAD) related, heart failure (HF) related, vascular-related, and non-cardiovascular rehospitalization. The primary outcome was the composite endpoint of cardiovascular death or cardiovascular rehospitalization. Classification of the endpoints was undertaken by the local investigators with no central validation. However, guidance for classification was provided. All deaths were considered cardiovascular unless an unequivocal non-cardiovascular cause could be established. All events were recorded in the electronic case report form (e-CRF).

Registry organization

The registry was conducted by an independent Executive Committee who formulated and implemented the study protocol. A Steering Committee with the chairperson of the Executive Committee and each National Coordinator of the study provided national feedback on the protocol and oversaw the study implementation. National coordinators, in conjunction with local centres, or participating centres depending on whether they are country/centre based, managed the approvals of national or regional ethics committees or Institutional Review Boards, according to local regulations. Operational coordination of the study and statistical analyses were carried out by the EORP Department.

Data quality was monitored by the ESC EORP Registry Project and Data Management teams. Data Quality Control followed a Data Validation Plan (DVP) defined by the Registry Executive Committee team in collaboration with the EORP team. This DVP listed all different types of data verification that were performed online and/or by sending messages to investigators in order to confirm or correct values when necessary. The checks allowed the detection of inconsistent values, protocol non-adherence, cross values not matched, incorrect chronology, missed values, out of range values and invalid values. The quality of data, consecutiveness of recruitment and key parameters were monitored according to a risk-based strategy (e.g. number of patients enrolled, issues, high number of data management queries) supervised by the ESC EORP.

Statistics

Analysis were performed among the population that completed, at least, the one-year follow-up. One-year follow-up data were analyzed up to 400 days to include patients with delayed follow-up information. Events occurring after 400 days among patients with more than one year of follow-up were censored to only report the one-year outcomes of the overall cohort. Continuous variables were reported as mean ± standard deviation (SD) 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 counts and percentages. Among-group 2x2 comparisons were made using a Chi2 test or Fisher's exact test if any expected cell count was <5. When more than 2x2 comparisons, the Monte-Carlo estimate of the exact P-value was used.

Paired data were analyzed using the McNemar-Bowker test. Plots of the Kaplan–Meier curves for time to composite events were performed. Composite events were CV mortality and/or CV rehospitalizations, HF mortality and/or HF rehospitalization, mortality and/or rehospitalization. A multivariable Cox regression analysis was performed to identify the independent predictors of each composite. Cox models were also performed with age, sex and region forced in the model.

Significance levels of 0.05 were required to allow a variable to stay within the model. Co-linearity between all candidate variables (variables with p<0.05 in univariable) within the model and variables considered of relevant clinical interest were tested before proceeding to the multivariable model. Variables include in the model were Age, heart rate, diabetes mellitus, past smoker, history of heart failure, atrial fibrillation previous stroke/TIA, chronic kidney disease, significant liver disease, COPD/asthma Malignancy, Hemoglobin, anemia, S-Creatinine, BNP, CRP , HDL, Ejection Fraction. Model fit was estimated using the Goodness of fit test proposed by May and Hosmer. In addition, the proportional hazard ratios assumptions were verified graphically and with the Schoenfeld residuals test. Missing data were not imputed. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Characteristics of the population

Overall, the CICD-LT registry enrolled 9174 patients with CCS across 154 centers from 20 countries between 1 May 2015 and 31 July 2018. The data-cutoff date of this interim analysis was December 31, 2019. One-year follow-up data were available for 6655 (72.5%) of patients. Baseline characteristics of patients included in the follow-up analysis and of patients with unknown status at one year are provided in the **table 1 and supplemental table 1**. In the follow-up population, the median age was 67 years and 73% were men. Among them, 23.9% had hypertension and 40.4% had hypercholesterolemia, 30.2% had diabetes mellitus, 19.6% had had previous non-urgent coronary revascularization and 36.5% a previous ST-segment elevation myocardial infarction (STEMI). **Supplementary table 2 and Supplemental Figure 1** shows drug treatment at discharge and at one year among survivors. The rate of recommended treatment, including the number of lipid lowering agents (6045 (95.4%) vs 5816 (91.8%), p<0.001), decreased between baseline and one year.

At one year, 83.3% (n=2226) of the follow-up population with complete information on cardiovascular risk factors had still at least one modifiable risk factor not at target according to current guidelines, including glycemia > 7mmol/l or low-density lipoprotein-cholesterol (LDL-C) > 1.81 mM/l or blood pressure above 140/90 mmHg. Finally, at one year, two thirds of the population had a LDL-C > 1.81 mM/l. The rate of patients with cardiovascular risk factors at target varied across the ESC regions, Southern Europe being the region with the lowest number of patients with uncontrolled risk factors at one year, **table 2**. At one year, women and elderly were still more likely to have uncontrolled risk factors compared with men and patients < 75 years old, **Supplemental table 3.**

Outcomes

Overall, 168 patients (2.5%) died during the first year of follow-up, cardiovascular death being the main cause of death (n= 97, 1.5%). Northern Europe had the lowest cardiovascular mortality rate, while southern Europe had the highest mortality rate (0.5% vs 2.0%, p value = 0.04). Of importance, women had a significantly higher rate of cardiovascular mortality compared to men (2.0% vs 1.3%, p value 0.02). During the follow-up period, 1606 patients (27.1%) were hospitalized at least one time, mostly for cardiovascular reasons (n=1220, 20.6%). CAD related hospitalization was the main cause for hospitalization (n=661, 11.2%), then heart failure (n=276, 4.7%) and vascular causes (n=117, 2.0%). The incidence of the composite primary outcome of cardiovascular death or cardiovascular hospitalization was significantly higher among Northern and Eastern Europe compared with Western and Southern Europe and was mainly driven by the number of hospitalizations **Figure 1**. Kaplan Meier curves for all cause of mortality and all cause of hospitalization according to regions are shown in **supplemental Figure 2**.

Association between baseline characteristics and one-year outcomes

In univariate analysis, patients who died or were hospitalized for cardiovascular causes were older, had a higher baseline heart rate, a lower hemoglobin, a higher serum creatinine, a higher CRP and were more likely to have diabetes, heart failure, atrial fibrillation, stroke peripheral revascularization, chronic kidney disease, malignancy, or chronic obstructive pulmonary disease (COPD or asthma) (**table 1**). The Cox model identified 7 variables independently associated with an increased risk of cardiovascular events: age (by 10 years, HR=1.08, confidence interval (CI) [1.02-1.16]), atrial fibrillation (HR=1.23, CI [1.05-1.44]), stroke/TIA (HR=1.60, CI[1.32-1.95]), severe liver disease (HR=1.70, CI[1.12-2.58], COPD/asthma (HR=1.33, CI[1.08-1.64]), elevated serum creatinine (per ten mmol/l, HR=1.02, CI[1.01-1.04]), impaired left ventricular function (left ventricular ejection fraction [LVEF] <40%), HR=1.85, CI[1.58-2.16]), **Figure 2**

The Cox Models for all-cause mortality and rehospitalization are displayed in **supplemental Figure 3**. When forced in the model, age, sex and region did not change the results (**supplemental Figure 4 and 5**).

DISCUSSION

This one-year analysis of the EORP CICD LT registry i/ confirms the relatively low rate of cardiovascular mortality of patients with chronic coronary syndrome observed in recent randomized trial enrolling patient with stable coronary artery disease (3,4). ii/ This rate varied slightly across the different regions of Europe and this finding reinforces the role of the ESC to homogenize the treatment of CCS. iii/ In contrast, the rate of hospitalization was high, one out of five patients being hospitalized for cardiovascular reason within one year. This highlights the need for a better monitoring and control of cardiovascular risk factors. This was particularly true for women and elderly patients that are known to less likely receive guidelines directed medical therapy and are, therefore, exposed to an increased cardiovascular

mortality (11,12). iv/ Finally, this analysis identified non-cardiac comorbidities associated with an increased risk of cardiovascular outcomes, including renal failure, liver disease, COPD or asthma, suggesting that a global approach of these patients with multiple diseases is warranted.

The EORP CICD LT registry provides unique and contemporary patient-level information across 20 ESC member or affiliated countries about the treatments and clinical outcomes of patients with CCS. While enrolling an all comers, unselected, population, the rate of cardiovascular mortality is similar to the one-year mortality rate of the recent COMPASS trial and, thus, relatively low (4). This is likely the result of an aggressive approach of the disease as proven by the high rate of guidelines recommended therapy prescription: 9 out 10 patients being treated with statin, betablockers and antiplatelet therapies. However, and despite these treatments, a vast majority of the participants have still uncontrolled risk factors and a high risk of hospitalization. In addition, one out five patients was an active smoker and one out three patients had a BMI $\geq$ 30 (table 1). While the proportion of patients with weight loss or smoking cessation at one year remains unknown, it can be reasonably hypothesize that this rate remains low, adding risk factors to hypercholesterolemia, high blood pressure and uncontrolled diabetes. The decline over time in the rate of prescription of recommended medications including aspirin, beta blockers, ACE inhibitors and statins is a concern and highlights the need for a tight monitoring of CCS patients (14). This finding was also observed at the 6 months follow-up of the pilot phase of the EORP CICD registry (10).

Considering that two thirds of the population with available laboratory values at one year had a LDL>1.81 mmol/L, while statins were prescribed in 9 out of 10 patients of the registry, there is also room for improvement by up titrating statins or considering proprotein convertase subtilisin/kexin type 9 inhibitors to reach the new recommended LDL target of 1.4mmol/ L

(15,16), in the cases of documented intolerance to statins or in the patients who are not at target despite a treatment with a statin at the maximal recommended dosage plus ezetimibe.

Considering the high number of patients with high level of LDL and the high rate of treatment with statins, it remains to determine whether the use of high dose of statins was associated with lower event rates regardless of achieved LDL-cholesterol levels or not.

Differences between men and women have also been studied in observational cohorts of patients with stable coronary artery disease (17,18). It has been demonstrated that women with such disease are, on average, older than men with higher rates of cardiovascular risk factors and are less likely to receive optimal medical treatment or coronary revascularization for their condition (19). Despite these differences, a prior analysis of the CLARIFY registry did not report any difference in one-year outcomes between men and women, with or without adjustment for possible confounders (11). In our registry, after adjustment for other variables, sex was not independently associated with the composite outcomes of cardiovascular death or rehospitalization. However, women were exposed to a relative increased risk of CV mortality of 50% compared with men in our study. Whether this increased mortality is explained by confounders certainly deserves further investigations.

We, finally, identified a number of clinical factors associated with the occurrence of cardiovascular death and/or cardiovascular hospitalization. While some discrepancies in the events rates were observed between the different regions of Europe, they were not independently associated with an increased risk of events when adjusted for other variables, suggesting that lifestyle and comorbidies overcome the potential difference between healthcare organization across European countries. The multivariate Cox analysis showed that a number of clinical factors were independently associated with the primary outcome: age, atrial fibrillation, stroke liver disease, COPD/Asthma, creatinine and a LVEF <40%. This highlights the importance of

comorbidities which may help identify a subgroup of patients at higher risk of hospitalization from cardiovascular causes. Interestingly, and as shown in the pilot phase of the registry, traditional cardiovascular risk factors such as smoking and hypercholesterolemia were not independent predictors of events at one-year follow-up in our cohort (7). This holds true in particular for diabetes mellitus, which was a strong predictor of all-cause and cardiovascular death in the REACH registry (20). This result might be explained by the proportion of elderly patients in our cohort (median age 67 y/o), in which the presence of comorbidities, such as stroke or heart failure, may have a greater impact than smoking and hypercholesterolemia, as compared with younger patients, on one year outcomes.

Limitation

Selection of centers was made on a voluntary basis and a center bias regarding the clinical profile and the treatment of patients enrolled cannot be excluded. Outcomes were not adjudicated, but reported by the local investigators. ICD codes were not used and, therefore, variation of definitions among investigators regarding assessment of cardiovascular death or hospitalization cannot be excluded, although guidance was provided. Of importance, since death from unknown causes were considered as cardiovascular death, the estimated rates may have been inflated. The main limitation of this analysis is related to the important number of missing data, one in three patients (2519, 27.4%) having an 'unknown status' (including loss of follow-up) at the interim one year follow-up, and limit therefore the interpretation of our conclusions.. Moreover, this finding also highlights the fact that clinical follow-up of patients with CCS is suboptimal. Since readmitted patients are more likely to be followed up, the rate of rehospitalization may be overestimated. In addition, there were significant differences between patients with and without follow-up regarding age, sex and comorbidities that limit the validity of the study results with respect to mortality and hospitalization rates as well as risk factor control. Another limitation is

the variable inclusion rate across the four regions, therefore potentially influencing outcomes. One-year LDL or glycemia data were not available in many patients and the interpretation of the CV risk factors control should be, therefore, interpreted with caution. Moreover, since patients were enrolled and followed-up before the implementation of the 2019 ESC guideline LDL-c target of 0.55g/L, this analysis overestimated the number of patients with a LDL-c level within the recommend range. The number of patients enrolled in Northern European countries was limited, making comparison with the other contributing regions difficult and cannot be, therefore, considered as representative of all the north of Europe. Finally, quality control was performed by queries following coherence of data checks and there was no systematic or random auditing of the data.

Conclusion

Despite an overall low cardiovascular mortality rate, patients with CCS are exposed to a high risk of CV hospitalization. Of importance, the rate of patient with uncontrolled risk factors at one year of enrollment is high, suggesting that there are still opportunities to improve the situation. In particular, health care providers should focus their effort in two populations of patients exposed to an increased risk of outcomes: women and elderly patients. Finally, this analysis identified non-cardiac comorbidities associated with an increased risk of cardiovascular outcomes including renal failure, liver disease, COPD or asthma, suggesting that a global approach of these patient is warranted.

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were performed by CL. Scientific activities were coordinated and supervised by APM, EORP Scientific Coordinator. A complete list of the CICD Investigators is provided in Appendix 1.

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Conflict of interest statement

Mathieu Kerneis report research grants from institut servier, federation francaise de cardiologie and consulting fees from Bayer, Kiniksa, Sanofi, Servier. Francesco 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 personal fees from Servier International, grants and personal fees from Novartis, personal fees from Merck Serono, personal fees from Boehringer Ingelheim, personal fees from Sunpharma, personal fees from Lupin, personal fees from Doc Generici, personal fees from Pfizer, personal fees from Spa Prodotti Antibiotici, outside the submitted work; and Director of Art Research and Science S.r.l. (A.R.S.1).

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"Authorship: MKo, RF, APM, PGS, LT, CPG contributed to the conception or design of the work. MKe, FC, RF, JLG, EK, CL APM, HR, PGS, JM, LT, MV, CPG, MKo contributed to the acquisition, analysis, or interpretation of data for the work. MKe and MKo drafted the manuscript. FC, RF, JLG, EK, CL APM, HR, PGS, JM, LT, MV, CPG critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy."

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Figure Legends

Figure 1: Kaplan-Meier curves for cardiovascular mortality and/or cardiovascular rehospitalization censored at 400 days by Region

Figure 2: Final Cox Regression Analysis for CV mortality and/or CV rehospitalization censored at 400 days - Forest plot with Hazard Ratio

Table 1 : Demographics and other baseline characteristics by CV mortality and/or CV rehospitalization censored at 400 days

	CV mortality and/or CV rehospitalisation (n =1257)	**No CV mortality and no CV rehospitalisation (n =4669)**	**P-value**
Type of documented CICD			
Previous STEMI	460 (36.6%)	1724 (36.9%)	0.1546
Previous NSTE ACS	283 (22.5%)	1094 (23.4%)	
Previous coronary revascularization	274 (21.8%)	890 (19.1%)	
Stable coronary artery disease	240 (19.1%)	961 (20.6%)	
Age (years) at inclusion			
Median (IQR)	69.0 (62.0-77.0)	68.0 (60.0-75.0)	<0.0001
Age >= 75 years	380 (30.4%)	1232 (26.4%)	0.0058
Male	919 (73.1%)	3424 (73.3%)	0.8733
Hypertension*	315 (25.1%)	1123 (24.1%)	0.4469
Heart rate (bpm)			
Median (IQR)	70.0 (62.0-78.0)	68.0 (62.0-75.0)	0.0006
Diabetes mellitus	449 (35.7%)	1364 (29.2%)	<0.0001
Current smoker	212 (16.9%)	875 (18.7%)	0.1273
Past smoker	473 (37.6%)	1617 (34.6%)	0.0484
History of heart failure	738 (58.7%)	2118 (45.4%)	<0.0001
History of atrial fibrillation	295 (23.5%)	665 (14.2%)	<0.0001
Previous stroke/TIA	136 (10.8%)	268 (5.7%)	<0.0001
Chronic kidney disease	143 (11.6%)	262 (5.7%)	<0.0001

	CV mortality and/or CV rehospitalisation (n =1257)	No CV mortality and no CV rehospitalisation (n =4669)	P-value
Significant liver disease	27 (2.2%)	48 (1.0%)	0.0015
COPD/asthma	115 (10.0%)	279 (6.4%)	<0.0001
Malignancy	82 (7.0%)	208 (4.9%)	0.0039
Hb1Ac (%)			
N	215	688	
Mean ± SD	7.49 ±1.51	7.38 ±1.39	0.4251
Hb1Ac >7%	114 (53.0%)	357 (51.9%)	0.7715
Hemoglobin (mmol/l)			
Mean ± SD	8.40 ±1.09	8.59 ±1.02	<0.0001
WHO anemia**	313 (26.7%)	845 (20.3%)	<0.0001
S-Creatinine (µmol/l)			
Mean ± SD	104.48 ±79.82	92.65 ±39.13	<0.0001
BNP (pmol/l)			
Mean ± SD	128.89 ±246.45	63.51 ±145.30	<0.0001
CRP (mg/l)			
Mean ± SD	3.98 ±10.1	2.03 ±6.9	<0.0001
LDL (mmol/l)			
Mean ± SD	2.54 ±1.10	2.54 ±1.05	0.7860
LDL > 1.81 mmol/L	596 (73.0%)	2262 (73.0%)	0.9674
HDL (mmol/l)			
Mean ± SD	1.17 ±0.41	1.19 ±0.39	0.0428

	CV mortality and/or CV rehospitalisation (n =1257)	No CV mortality and no CV rehospitalisation (n =4669)	P-value
Triglycerides (mmol/l)			
Mean ± SD	1.55 ±0.80	1.63 ±1.00	0.2764
BMI >=30kg/m²	447 (35.7%)	1585 (34.2%)	0.3103
Ejection Fraction	1136 (90.4%)	4084 (87.5%)	0.0056
Mean ± SD	50.04 ±13.94	53.37 ±10.61	<0.0001
Median (IQR)	52.0 (40.0-60.0)	55.0 (48.0-60.0)	<0.0001
EF <40%	243 / 1136 (21.4%)	395 / 4084 (9.7%)	<0.0001

Table 2: Risk Factors at Follow-Up by Region

	All (n =6655)	Western Europe (n =1059)	Southern Europe (n =2223)	Eastern Europe (n =3174)	Northern Europe (n = 199)	P-value
Patients with						
Glycemia > 7mmol/l	476 (20.6%)	53 (27.0%)	162 (23.5%)	252 (18.2%)	9 (20.9%)	0.0043
LDL > 1.81 mM/l	1434 (66.5%)	145 (60.2%)	413 (59.7%)	840 (71.5%)	36 (76.6%)	<0.0001
SBP > 140 mmHg or DBP > 90 mmHg	873 (16.8%)	129 (26.0%)	187 (11.6%)	504 (17.4%)	53 (29.0%)	<0.0001
Glycemia > 7mmol/l OR LDL > 1.81 mM/l OR SBP > 140 mmHg OR DBP > 90 mmHg	2226 (83.3%)	265 (89.5%)	610 (76.7%)	1268 (85.0%)	83 (93.3%)	<0.0001
Patients with baseline and follow-up data						
Glycemia > 7mmol/l						
Baseline	522 (25.0%)	30 (27.8%)	195 (29.4%)	282 (22.0%)	15 (38.5%)	0.0006
1yr F-up	436 (20.9%)	32 (29.6%)	159 (24.0%)	238 (18.6%)	7 (17.9%)	0.0043
LDL > 1.81 mM/l						

	All (n =6655)	Western Europe (n =1059)	Southern Europe (n =2223)	Eastern Europe (n =3174)	Northern Europe (n = 199)	P-value
Baseline	1173 (72.2%)	117 (70.9%)	413 (69.1%)	609 (74.2%)	34 (85.0%)	0.0473
1yr F-up	1035 (63.7%)	99 (60.0%)	340 (56.9%)	565 (68.8%)	31 (77.5%)	<0.0001
SBP > 140 mmHg or DBP > 90 mmHg						
Baseline	1215 (23.4%)	176 (35.4%)	309 (19.2%)	667 (23.0%)	63 (34.4%)	<0.0001
1yr F-up	873 (16.8%)	129 (26.0%)	187 (11.6%)	504 (17.4%)	53 (29.0%)	<0.0001
Glycemia > 7mmol/l OR LDL > 1.81 mM/l OR SBP > 140 mmHg OR DBP > 90 mmHg						
Baseline	1927 (88.0%)	213 (92.6%)	586 (85.3%)	1049 (88.1%)	79 (96.3%)	0.0020
1yr F-up	1801 (82.2%)	205 (89.1%)	510 (74.2%)	1010 (84.8%)	76 (92.7%)	<0.0001

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

Chi-2 or Fisher exact test [a] is used for binary variables. Monte Carlo estimates of the exact p-values is used for qualitative variables with more than 2 possibilities

LDL= Low Density Lipoprotein – SBP= Systolic Blood Pressure – DBP= Diastolic Blood Pressure

Figure 1: Kaplan-Meier curves for cardiovascular mortality and/or cardiovascular rehospitalization censored at 400 days by Region

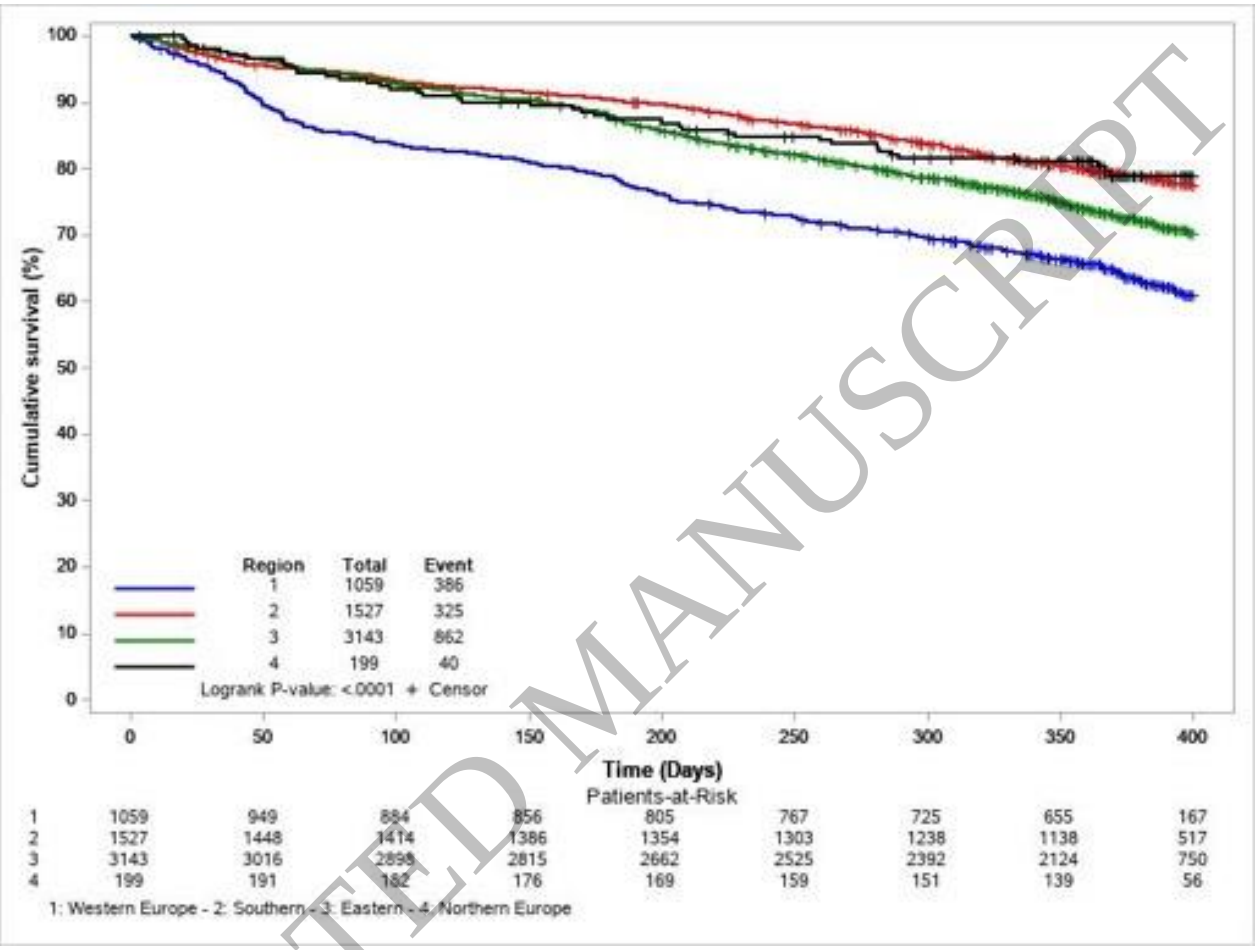

Figure 2: Final Cox Regression Analysis for CV mortality and/or CV rehospitalization censored at 400 days - Forest plot with Hazard Ratio