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## Treatment and outcomes of chronic coronary syndromes: the EORP EURECA imaging registry

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## Abstract

**Purpose:** To evaluate the impact of patients' characteristics and results of non-invasive diagnostic tests on downstream therapeutic strategies in the EURECA population.

**Methods and results:** In 4175 patients with chronic coronary syndrome (CCS), we analysed the association of clinical characteristics, exercise electrocardiogram (ECG), stress imaging and computed tomography coronary angiography (CTCA) results with early treatment choices (within 6 months from enrolment) categorized as: 1. no treatment change; 2. intensified medical treatment (IMT, i.e. new therapy or increase of previous therapy); 3. revascularization (plus IMT). MACE (cardiac death, non-fatal myocardial infarction, coronary revascularization, or hospitalization for cardiac reasons) at 6-month follow-up were recorded.

**Results:** No treatment change, IMT or revascularization were received by 60.9%, 25.2%, and 13.9% of patients, respectively. At logistic regression analysis, enrollment in cardiovascular departments, typical angina, positivity of exercise ECG and of any imaging test were major predictors of IMT. Older age, male sex, moderate/severe ischemia at stress imaging and severely obstructive CAD (>70% stenosis in one major coronary vessel) at CTCA were additional determinants of revascularization. Medical treatment was intensified in only 18.6% and 35.1% of patients with no CAD and non-obstructive CAD, respectively. Revascularization was performed in most patients with obstructive CAD (61.0%), independently of underlying inducible ischemia. MACE occurred in 2.6% of patients, with the worst outcome in patients with both obstructive CAD and ischemia (9.1%).

**Conclusions:** In patients with CCS, the choice to intensify medical treatment was largely suboptimal. Revascularization was guided mostly by the anatomical rather than by the functional disease phenotype. Short-term outcomes mirror non-invasive imaging risk profiles.

## INTRODUCTION

Among cardiovascular diseases, ischemic heart disease is still the major cause of death and morbidity worldwide<sup>1-3</sup>. On the other hand, coronary artery disease (CAD) incidence is steadily declining in many European countries, likely due to the more effective implementation of lifestyle recommendations, pharmacological and therapeutic interventions designed to achieve prevention, stabilization, or regression of the disease<sup>2,4</sup>. Nevertheless, the implementation of adequate treatments in patients with CAD in daily clinical practice is still insufficient<sup>5</sup>. For this reason, existing European Society of Cardiology guidelines (GL) for cardiovascular disease prevention and for the management of chronic coronary syndromes (CCS) have recommended the use of preventive, diagnostic, and therapeutic strategies targeted to patients with specific disease phenotypes<sup>4,6</sup>. Accordingly, intensified medical therapy (IMT), aimed at addressing major cardiovascular risk factors is advocated in all patients with any documented CAD, who are attributed to a very high 10-year cardiovascular mortality risk<sup>4</sup>. On the other hand, invasive interventions – including coronary revascularization– are indicated in patients with more severe disease phenotypes, namely functionally significant coronary lesions, at a predicted highest risk of major adverse cardiac events (MACE)<sup>6,7</sup>. However, the adoption of GL recommendations is still largely sub-optimal, as recently documented by the results of the EURECA registry gathering data from >5000 patients with suspected or known CAD from 73 centers in 24 ESC-member countries<sup>8</sup>. In as much as 44% of those patients, the diagnostic strategies were in disagreement with the GL recommendations mainly because a significant proportion of patients were referred to invasive coronary angiography (ICA) without previous recognition of a high-risk CAD phenotype (i.e., without downstream severe inducible ischemia). Indeed, non-adoption of GL recommendations was associated with a lower utilization of non-invasive imaging tests and a higher proportion of invasive procedures performed<sup>8</sup>. Understanding the interaction between patients' clinical risk profiles, results of non-invasive diagnostic tests, and downstream therapeutic choices in common clinical practice is complex but may unveil divergence with GL recommendations and the possible impact on patients' prognosis. Accordingly, we aimed to assess the major determinants of patients' management strategies in the contemporary population of patients with suspected or known CCS enrolled in the EURECA registry and to determine the possible prognostic impact of different management choices at a short-term follow-up.

## MATERIALS AND METHODS

The enrollment criteria of the EURECA registry have been previously described in detail<sup>8</sup>. Briefly, consecutive patients with suspected or known CCS were enrolled between May 2019 and March 2020 in 73 centres from 24 ESC-members or affiliated countries.

Baseline clinical data, quality of life (QoL) information [namely the Visual Analog Scale (VAS) self-reported score and the composite time trade-off (cTTO) model], and results of non-invasive tests performed during the diagnostic work-up including exercise ECG, stress imaging, and computed tomography coronary angiography (CTCA) were registered and used as possible determinants of downstream treatment strategies. Results of invasive coronary angiography (ICA), when performed, early treatment choices including coronary revascularization (within 90 days from enrolment) and short-term follow-up information (until 6 months from early treatment) were also registered. Moreover, in each patient, the adoption of ESC GL recommendation on CCS regarding the overall diagnostic process was recorded based on previously published criteria<sup>8</sup>.

Patients with unstable cardiac conditions [i.e., acute coronary syndrome or recent (<6 months) hospitalization for any cardiac disease], any other severe cardiac disease (i.e. significant valvular disease or arrhythmia, and severe heart failure), significant comorbidities (i.e. cancer), and inability to provide informed consent were excluded from the EURECA registry.

Of the total 5156 patients enrolled in the EURECA registry, 4175 patients (81.0%) with available information on early treatment strategies and 6-month follow-up were included in the present sub-analysis (**Figure 1**).

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.

### **Tests protocols**

Standard acquisition and interpretation protocols, shared among all centres before the initiation of the registry, were used for each diagnostic test, and the criteria adopted for the categorization of positivity and severity of stress imaging, CTCA, and ICA results have been detailed previously<sup>8</sup>. In particular, at stress imaging tests moderate-to-severe inducible ischemia was defined by the presence of stress-induced wall motion abnormality in at least 2/16 myocardial segments, stress-induced perfusion defect  $\geq 10\%$  of LV myocardium (or summed difference score  $\geq 7$ ); other non-negative results included evidence of mild inducible ischemia, old myocardial infarction, or an uncertain test. At CTCA and ICA a severely obstructive CAD was defined by the presence of occlusive or severely obstructive lesions ( $\geq 70\%$  stenosis) in at least one major coronary vessel or occluded/obstructed grafts/stents; other non-negative results included evidence of moderate obstructive (50-69% stenosis) or non-obstructive ( $< 50\%$  stenosis) lesions in at least one major coronary vessel or non-obstructed grafts/stents. A negative CTCA or ICA was defined as the absence of any lesion of main vessels but could include stenoses in minor branches.

Exercise ECG was categorized as positive, with evidence of old myocardial infarction or uncertain results, and negative.

Adoption of 2019 ESC Guidelines for the use of non-invasive imaging and ICA in the management of patients was defined as previously published<sup>8</sup>.

### **Clinical management**

Patient management followed local routine clinical practice, which included prescribing medications and determining the need for diagnostic and therapeutic procedures. Early treatment received by each patient was classified as: 1. no change in treatment; 2. intensified medical treatment (IMT), which involved adjusting medication dosages or adding new drugs; 3. coronary revascularization (in addition to IMT).

Moreover, after completing the diagnostic process, investigators were tasked with adjudicating a disease phenotype for each patient based on the presence or absence of non-obstructive or obstructive CAD as determined by anatomical imaging, and the presence or absence of inducible ischemia documented during functional stress tests. CAD phenotypes were adjudicated in 3819 out of 4175 (91.5%) patients and further categorized into 5 groups: 1. no CAD; 2. non-obstructive CAD without documented ischemia; 3. non-obstructive CAD with

documented ischemia; 4. obstructive CAD without documented ischemia; 5. obstructive CAD with documented ischemia.

### **Follow-up**

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.

The primary endpoint was the occurrence of MACE, including cardiac death, non-fatal myocardial infarction, late coronary revascularization (after 90 days from the completion of the diagnostic process), or hospitalization for other cardiac reasons (unstable or recurrent angina or heart failure). Secondary endpoints included all causes of death and the combination of cardiac death and non-fatal myocardial infarction.

### **Statistical analysis**

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  $\chi^2$  test or 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.

Backward multinomial logistic regression analyses were used to determine the factors associated with each possible therapeutic strategy – namely no treatment, IMT, or revascularization – including in 2 incremental models all relevant variables with  $P < 0.05$  in univariable analysis. Logistic regression analysis for the 1<sup>st</sup> model included variables related to characteristics of the enrolling centres, demographic and clinical characteristics of the patients, diagnostic test results, and QoL variables, and the 2<sup>nd</sup> model also added the adoption of GL recommendations for the use of imaging. Cox regression analysis was used to assess the association between baseline clinical and diagnostic tests with treatment covariates and the risk of MACE. Variables with  $P < 0.05$  at univariable analysis were included as in the multivariable models. 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**

### **Clinical characteristics of the study population**

**Table 1** summarizes the characteristics of the patient population and subgroups based on early treatment choices. Most patients were enrolled in university centers and cardiovascular departments. The mean age was  $63.5 \pm 11.3$  years, with 39.9% females. Prevalent risk factors were hypertension, dyslipidemia and smoking habits while family history, obesity, and diabetes were less frequent.

Typical angina was reported by 26.5%, previous CAD was known in 27.0% (23.7% previously revascularized), and 5.1% had left ventricular dysfunction (ejection fraction  $< 50\%$ ). Quality of life scores averaged  $71.0 \pm 19.1$  (VAS) and  $0.801 \pm 0.203$  (Index, cTTO model).

Early treatment choices included: no change in medical treatment for 60.9%, intensified medical treatment (IMT) for 25.2%, and coronary revascularization for 13.9% (86.9% PCI, 13.4% CABG).

Patients receiving IMT, as compared with patients in whom medical treatment was left unchanged, were more frequently enrolled in cardiovascular departments, were older, had a higher prevalence of all cardiovascular risk factors and worse clinical presentation (more frequent typical symptoms, left ventricular dysfunction, lower QoL scores). Patients who were revascularized further differed from patients receiving only IMT, because they were even older, less frequently females, had a higher prevalence of more common risk factors (hypertension, dyslipidemia, and smoking) and even worse clinical presentation (typical angina and previous CAD).

### **Use and results of non-invasive tests and invasive coronary angiography**

The use and results of non-invasive tests and ICA in the overall population and subgroups of patients defined according to early treatment choices are reported in **Supplementary Table 1**. In the overall population stress imaging was the most used non-invasive test (42.8%) followed by exercise ECG (30.9%) and CTCA (26.2%) while ICA was performed in almost one-third of all patients (30.6%).

Stress imaging remained the most frequently used non-invasive test in each of the three subgroups of patients with a decreasing trend from patients in whom medical treatment was left unchanged, to those who received only IMT and to those who were revascularized ( $P < 0.01$  for trend). Exercise ECG was more frequently used in patients in whom medical treatment was left unchanged than in those who received IMT or revascularization ( $P < 0.01$  for both comparisons). CTCA was more frequently used in patients receiving IMT compared to the other two subgroups ( $P < 0.01$  for both comparisons). ICA was more frequently used in patients receiving IMT than in those with unchanged medical treatment, and it was obviously performed in all patients undergoing revascularization (**Figure 2**). The relative prevalence of the three treatment choices associated with the use and results of each test is shown in **Figure 3**. Following non-invasive tests, most patients were more likely to have no change in treatment than to receive IMT or revascularization. Conversely, patients undergoing ICA predominantly received revascularization or IMT (**Figure 3A**). Positive exercise ECG results or moderate/severe inducible ischemia on stress imaging led to similar frequencies of choosing no treatment change, IMT, or revascularization. In contrast, severely obstructive CAD detected via CTCA or ICA predominantly resulted in coronary revascularization (**Figure 3B**). Other non-negative imaging results and even negative findings on ICA (no obstructive disease in main coronary vessels) were most commonly followed by IMT.

### **Independent clinical and non-invasive tests determinants of treatment choices**

The results of the incremental multinomial logistic regression models exploring the independent variables associated with different treatment choices are reported in **Supplementary Table 2** and **Figure 4**. In the general model including both clinical and non-invasive test variables, being enrolled in a cardiovascular department, having a positive family history, reporting more severe symptoms and a lower QoL score, having had a positive exercise ECG and any non-negative imaging test results significantly increased the probability of

receiving IMT than no treatment change. Conversely, older age, male gender, and findings of moderate/severe ischemia at stress imaging or severely obstructive CAD at CTCA independently heightened the probability of undergoing coronary revascularization rather than receiving IMT alone or no treatment change. When the adoption of GL recommendations for the use of imaging was added to the model it decreased the probability of receiving either IMT or revascularization independently of all the other variables (**Figure 4**).

### **Interaction between disease phenotype and treatment choices**

In the 3819 patients in whom the disease phenotypes were reported, obstructive CAD, non-obstructive CAD, and no CAD were adjudicated as the final diagnosis in 24.7%, 38.5%, and 36.7% of patients, respectively. Any inducible ischemia was reported in 19.7% of patients.

A minority of patients with a final diagnosis of no CAD (267/1402, 19.0%) or non-obstructive CAD (517/1472, 35.1%) received IMT, more frequently those with inducible ischemia (58.9% vs 29.9%,  $P < 0.001$ ). The majority of patients with obstructive CAD (576/945, 61.0%) were revascularized (plus IMT) independently of absence or presence of inducible ischemia (61.1% vs 61.8%  $P = \text{NS}$ ) while a minority received only IMT (201/945, 21.3%) independently of absence or presence of inducible ischemia (21.4% vs 18.0%  $P = \text{NS}$ ) (**Central Figure**)

### **Follow-up and Prognosis**

As shown in **Table 2**, at 6-month follow-up, 64.7% of the overall population reported improved (or no) anginal symptoms, while in 35.3% symptoms were unchanged or worsened. Anginal symptoms had improved in significantly more patients receiving revascularization (75.7%) than in the other subgroups, receiving or not receiving IMT. Similarly, QoL indexes improved in the overall population significantly more in patients who had received revascularization.

During follow-up, additional imaging tests were performed in 5.7% of patients, mainly by stress-imaging (3.6%) and ICA (2.3%), with the highest proportion in patients who had received revascularization and with progressive lower proportions in patients who had received IMT or no treatment change.

MACE occurred in 110 patients, more frequently in patients receiving revascularization or IMT (5.0% and 4.3%, respectively) than in those treated conservatively (1.4%;  $P < 0.01$  vs both). A similar significant trend was demonstrated for any MACE component and for the secondary combined endpoint (cardiac death + non-fatal MI) (**Table 2**).

At univariable Cox regression analysis (**Table 3**) baseline demographic data, risk factors, worse clinical presentation and QoL measurements, positive results of non-invasive testing and ICA as well as a more intensive treatment either with IMT or revascularization were significantly associated with MACE. However, at multivariable Cox regression analysis, only a few clinical variables (previous history of CAD, reduced LV ejection fraction, and lower QoL score), positivity of exercise ECG, and any evidence of inducible ischemia or CAD at non-invasive imaging tests were independent predictors of MACE (**Table 3**). Demographic and metabolic risk factors, results of ICA, and treatment choices were not independently associated with outcome. Adherence to ESC Guidelines for the use of imaging did not affect outcome at 6 months.

When the presence and severity of anatomical CAD and ischemia were considered, a progressively higher event rate was observed in patients with non-obstructive or obstructive CAD and among them even higher in those with also documented ischemia (**Figure 5**).

## **DISCUSSION**

The present study, conducted in a large population of contemporary patients with suspected or known CCS enrolled in multiple ESC-member countries, yielded the following key findings: 1) being enrolled in a cardiovascular department, having a more severe clinical presentation, a positive exercise ECG and any non-negative imaging tests results significantly increases the probability of receiving IMT than no treatment change; 2) factors such as older age, male gender, and the presence of moderate/severe ischemia on stress imaging or severely obstructive CAD on CTCA further increases the probability of receiving revascularization (plus IMT); 3) nevertheless, the majority of patients diagnosed with non-obstructive CAD did not undergo any treatment change, while most patients diagnosed with obstructive CAD underwent revascularization, irrespective of the presence or absence of documented inducible ischemia (**Central Figure**).

In this population cardiac mortality at a short-term follow-up was relatively low but the frequency of the combined prognostic endpoint of MACE (cardiac mortality, non-fatal MI, late revascularization, and hospitalization for other cardiac reasons) was still high (2.6% at 6-month). MACE were associated with non-invasive evidence of either non-obstructive or obstructive CAD and ischemia at non-invasive tests **Figure 5** but were not influenced by more intense early treatment choices. On the other hand, early revascularization was more frequently associated with improvement of symptoms and better QoL scores at 6 months but with a higher rate of additional exams.

### **Predictors of coronary revascularization in the EURECA registry**

Current international guidelines for the management of patients with chronic CAD suggest intensification of medical treatment, in the presence of coronary atherosclerosis and/or myocardial ischemia, tailored to the individual clinical and disease risk profiles, to improve symptoms and outcome<sup>6,9</sup>. Guidelines also suggest proceeding towards coronary revascularization only in subjects with very high-risk left main and multivessel obstructive CAD to improve outcome. Revascularization of obstructive CAD with underlying severe ischemia is also advised mainly to improve symptoms<sup>6,7,9</sup>. These recommendations are supported by evidence suggesting that anatomy-guided treatment of stable CAD may not improve prognosis, prompting consideration of combined anatomical and functional assessments to guide medical and potentially interventional management in patients with persistent symptoms<sup>10-14</sup>.

In the EURECA population, we observed that in current clinical practice a higher perceived patient risk and a more severe clinical presentation (i.e., older age, male gender, typical angina, and positive exercise ECG), as well as high-risk results of any (anatomical and/or functional) imaging test, drive coronary revascularization rather than IMT. Interestingly, it seems that an obstructive CAD at anatomic testing is frequently treated by coronary revascularization,

independently of any documentation of ischemia by proper stress non-invasive or invasive tests. In fact, in one in every four patients with anatomical obstructive CAD revascularization is performed despite the absence of any hemodynamically significant coronary lesion at non-invasive functional imaging or invasive iFR/FFR. Actually, iFR/FFR was measured only in 7.7% of all patients undergoing ICA and in 6.4% of patients receiving revascularization. On the other hand, only a positive exercise ECG was used to document inducible ischemia in 15.1% of patients receiving revascularization.

### **Intensification of medical treatment in CCS patients: recommendations vs clinical practice**

In patients with CCS, IMT is crucial for controlling symptoms, preventing CAD progression, and avoiding adverse events<sup>6,9</sup>. Accordingly, it is widely accepted that IMT should be systematically implemented also in patients with early signs of disease, such as those with non-obstructive CAD or mild-to-moderate ischemia, whereby it could avoid the progression towards more severe CCS manifestations<sup>4,15,16</sup>. Our data provide updated insights into the implementation of IMT in an everyday population of symptomatic patients with suspected or known CCS, demonstrating a consistent underutilization of intensified medical treatment. Prevention guidelines attribute a very high cardiovascular risk to patients with any documentation of atherosclerosis<sup>4</sup> and there is established evidence that inducible ischemia is associated with adverse prognosis<sup>17</sup>. Accordingly, the present data reinforce available evidence that, in current clinical practice, IMT is underutilized in patients at high and very high risk based on diagnostic testing, which could explain the frequent failure to achieve guidelines-directed goals for control of major cardiovascular risk factors (i.e., dyslipidemia and diabetes)<sup>18,19</sup>.

As expected, among patients enrolled in the EURECA registry, both a clinically perceived higher cardiovascular risk profile (male gender, higher symptoms burden, and risk factors profile) and any positivity of diagnostic tests portended towards IMT (**Figure 4**).

Nevertheless, even though the cardiovascular risk profile was relatively high in the EURECA population (**Table 1**), as much as 81.4% of patients with negative diagnostic tests, 66.5% of patients with non-obstructive CAD (with or without ischemia), and 19.1% of patients with obstructive disease (with or without ischemia) did not receive any change in medical treatment. The underutilization of intensified medical treatment was particularly evident in patients with non-obstructive CAD without inducible ischemia and to a lesser extent in those with documented ischemia

### **Impact of clinical profile, results of diagnostic tests, and treatment on prognosis**

In patients with CCS, the clinical and prognostic impact of the different treatment strategies – namely no treatment change, IMT, or revascularization – has been the subject of intense investigation<sup>20,21</sup>. While IMT addressing major cardiovascular risk factors, the atherosclerotic process and the mechanisms of ischemia is largely considered the initial treatment strategy in CCS patients<sup>6,9</sup>, coronary revascularization may be still advised in the case of recalcitrant symptoms possibly associated with high-risk diagnostic test findings and ischemia<sup>21,22</sup>. Our study shows that patients receiving coronary revascularization had a significant improvement in QoL measures and anginal symptoms status than those managed more conservatively, with only 24.3% of revascularized patients reporting unchanged (or worsened) symptoms at short-term follow-up (vs 37.8% and 36.8% of patients receiving IMT or no treatment change, respectively;  $P < 0.001$ ). On the other hand, revascularized patients also received more frequent additional diagnostic tests at follow-up than those receiving IMT or no change in treatment.

Specifically, ≈8% of revascularized patients received repeated stress-imaging and/or ICA within 6 months, a finding in line with available evidence showing a non-negligible rate of repeated testing in revascularized CCS patients, at large<sup>12,23-25</sup>. Of notice, in the EURECA population, IMT was not associated with a relevant impact on patients' symptoms status, which could be explained by possible underutilization of specific anti-ischemic drugs<sup>26</sup> in patients with documented inducible ischemia. However, the relatively low prevalence of typical angina and inducible ischemia (<30% for both) in our population of patients may have also diluted any possible effect of treatment, possibly warranting dedicated investigations.

Regarding the determinants of adverse outcome, in the present analysis, we took into account only adverse events occurring at a short 6-month follow-up. Nevertheless, the MACE rate that was observed in our registry was in the range of 5% per year, putting the EURECA population into (at least) a moderate-risk category. In the overall cohort, MACE concentrated in patients with progressively more severe clinical and imaging risk findings and peaked in the phenotype of patients with combined obstructive CAD and inducible ischemia (**Figure 5**), whereby close to 1 every 10 patients experienced an event. Interestingly, after multivariable correction, no impact of either management strategy on adverse events was observed, suggesting on one side that current treatment choices are not targeted to the patient risk and disease phenotype (**Central Figure**) and confirming, on the other hand, the available evidence on the inconsistent association between patients' treatment strategies and adverse events in unselected CCS patients.

### Limitations

The limitations of the present study merit consideration. Of the 5196 patients enrolled in the EURECA registry, complete follow-up data were available in 4175 (80.4%). The final diagnosis was annotated in 3819 of these 4175 patients and 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 judgment, 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. Finally, part of the enrolment period was coincident with the outbreak of the COVID-19 pandemic. However, adverse events related to COVID-19 were identified and excluded from the analyses. Very different health systems were also represented in the EURECA registry so costs and reimbursement policy could have affected the diagnostic pathways.

### Conclusions

Our study on contemporary patients with CCS across multiple countries reveals that treatment intensity correlates more with the perceived clinical risk and general imaging results than with specific high-risk disease phenotypes and guideline directives, leading on one hand to underutilization of intensified medical therapy and on the other to frequent coronary revascularization procedures irrespective of inducible ischemia. In such populations, early treatment choices do not consistently improve outcomes even if revascularization can improve

symptoms. Non-obstructive CAD patients are particularly undertreated, despite showing a high cardiovascular risk profile.

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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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## Figure legends

Figure 1. Flow chart of the study population. Of the whole EURECA population, 4175 patients (81.0%) had available information on both early treatment strategy (within 6-months from enrollment) and short-term follow-up. In 3819/4175 (91.5%) patients, information on the investigators' adjudicated disease phenotype, based on the presence or absence of non-obstructive or obstructive CAD as determined by anatomical imaging, and the presence or absence of inducible ischemia documented during functional stress tests, were also available.

Figure 2. Interaction between both non-invasive tests use and ICA with early treatment strategies. A comparison of the % of use of the different non-invasive tests (exercise ECG, stress imaging, and CTCA) among the different treatment strategies was performed: \* =  $P < 0.05$  vs exercise ECG; # =  $P < 0.05$  vs CTCA.

Figure 3. (A) The relative prevalence of the three treatment choices associated with the use of each test; (B) The relative prevalence of the three treatment choices associated with the results of each test; -: test result negative, +/-: test result uncertain, +: test results positive (see the Methods section for a full description of the criteria for tests' results interpretation)

Figure 4. Multinomial logistic regression analysis showing the variables significantly associated with the different patients' treatment strategies.

Figure 5. MACE rate at 6-months follow-up according to patients' disease phenotype. The lowest event rate was observed in patients with "no CAD" (0.6%) with progressively higher values in those with non-obstructive CAD (1.6% in the absence vs 6.8% in the presence of ischemia;  $P < 0.01$ ) and obstructive CAD (3.7% in the absence vs 9.1% in the presence of ischemia;  $P < 0.01$ ).

**Central Figure.** *The frequency of choosing IMT or revascularization (plus IMT) paralleled the severity of disease diagnosis, increasing from Group 1 (18.6% and 0%) to Group 2 (29.9% and 0.1%), to Group 3 (58.9% and 2.1%) to Group 4 (21.4% and 61.1%), or Group 5 (17.9% and 61.8%). IMT was more frequent in patients with non-obstructive CAD (35.1%) than in those with no CAD (18.6%) ( $P < 0.001$ ), even if still in 66.5% of them the treatment was left unchanged. Revascularization frequency was higher in patients with obstructive CAD but independent of the association of obstructive CAD with documented ischemia.*