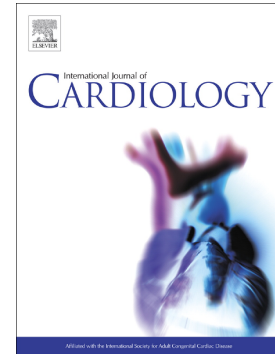


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Real-world implementation of ESC guidelines in chronic coronary syndromes: insights from the EURECA registry with a focus on Italian practice

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Introduction

The EURECA registry showed that 2019 ESC guideline adoption (GA) for management of Chronic Coronary Syndromes is suboptimal regarding the use of diagnostic tests. The present sub-analysis compared Italian cohort (IC) versus non-Italian cohorts (NIC) and explored Italian regional differences.

Methods

Patients were grouped into NIC and IC, this further stratified in Northern, Central, and Southern regions. GA was assessed for the choice of first diagnostic test (Endpoint-A) and for the overall diagnostic pathway (Endpoint-B). Quality-of-life, additional diagnostic test and MACE were assessed at 6-month.

Results

Among 4,262 patients, 38.4% (1,636) were enrolled in Italy (May-2019/March-2020). GA was suboptimal in both cohorts but higher in Italy ($p < 0.001$ for Endpoint-A and -B). In IC vs. NIC exercise-ECG and coronary-CT-angiography were used more frequently (39.6% vs. 25.5%, 35.0% vs. 20.2%; $p < 0.001$) while stress-imaging and invasive coronary angiography (ICA) were less used (39.4% vs. 45.9%, 22.9% vs. 34.5%; $p < 0.001$ for both). Exercise-ECG and ICA remained the main drivers of non-GA in both cohorts. Final diagnosis of obstructive-CAD was less frequent in IC than NIC (19.9% vs. 26.9%; $p < 0.001$), with similar rate of ischemia detection (19. % vs. 18.9%; $p = 0.74$) and revascularization (12.8% vs. 14.0%; $p = 0.27$). GA, obstructive-CAD, ischemia, treatment changes and revascularizations were low in Italian-southern region. Six-month MACE was low and not associated with GA in both cohorts.

Conclusions

The rate of GA was higher in IC as compared with the NIC but still suboptimal, especially in Italian-southern region. Non-GA was mainly driven by exercise-ECG and ICA as first test use.

INTRODUCTION

In contemporary clinical practice, the recommendations outlined in the 2019 ESC Guidelines in term of diagnostic tests for the diagnostic assessment of Chronic Coronary Syndromes (CCS) (1) have not been fully implemented, as evidenced by findings from the EURECA registry (2). Non-adoption of these recommendations has been associated with a higher proportion of invasive coronary angiographies (ICA), accompanied by a lower diagnostic and therapeutic yield of these procedures. In addition, it has been linked to a greater use of downstream diagnostic testing and a shorter time to late revascularization during follow-up (2). Multiple factors may have influenced this diagnostic landscape, given also the heterogeneity of healthcare systems across the 24 countries participating in the EURECA registry. Whether the large proportion of patients enrolled in Italy (38.4% of the study population) may have substantially influenced the findings of the EURECA registry remains to be explored. Thus, sub-analysis aimed to assess differences in the adoption of the 2019 ESC guideline recommendations for the use of non-invasive and invasive imaging modalities between the Italian cohort and the non-Italian cohort. In addition, we explored regional variations within Italy to identify potential geographic disparities in the diagnostic and therapeutic management of CCS.

METHODS

From the overall EURECA study population, we included patients with stable symptoms (angina, chest discomfort, or dyspnea), with or without known coronary artery disease (CAD), referred for elective diagnostic evaluation, who had complete 6-month follow-up and available data on guideline adoption. Study design and inclusion/exclusion criteria have been previously reported (2). The study population was divided into two cohorts: patients enrolled in Italian centers (Italian cohort) and those enrolled in other ESC member or affiliated countries (non-Italian cohort). The Italian cohort was further stratified by geographic area (Northern, Central, and Southern Italy). Diagnostic evaluation and patient management were performed according to local clinical practice at each enrolling center. Patients were stratified by previous CAD and pre-test probability (PTP), as in the main study. Six-month follow-up included quality-of-life (QoL) assessment, need for additional diagnostic testing, and major adverse cardiovascular events (MACE), defined as cardiac death, non-fatal myocardial infarction, late coronary revascularization, or hospitalization for unstable/recurrent angina or heart failure.

The primary objective of this ancillary analysis was to compare the rate of adoption of the 2019 ESC guideline recommendations for the use of non-invasive and invasive imaging in patients with known or suspected CCS, between the Italian and non-Italian cohorts and across geographical regions within Italy. Guideline adoption was assessed using two complementary endpoints: Endpoint A, reflecting concordance between the initial diagnostic test and guideline recommendations based on clinical presentation and pre-test probability; and Endpoint B, reflecting adherence across the entire diagnostic pathway, including the use of additional imaging tests (2).

The secondary objective was to compare Italian and non-Italian cohorts in terms of major adverse cardiovascular events (MACE) and their individual components during follow-up, as well as changes in medical therapy, quality of life (QoL), need for additional diagnostic testing, and symptoms.

Statistical Analysis

Continuous variables were compared using the Kruskal–Wallis test, and categorical variables using the chi-square test or Fisher’s exact test, as appropriate. Multinomial logistic regression with backward selection—including center characteristics, patient demographics, clinical variables, quality-of-life scores, and diagnostic test results—was used to identify factors associated with treatment strategies. Cox proportional hazards models were applied to assess the association between these variables and the risk of adverse events. Variables with a P-value ≤ 0.05 were retained in the final multivariable models. All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

Study population

Among the 5,156 patients enrolled in the main study, 4,262 completed the 6-month follow-up and were included in this analysis. Of these, 1,636 (38.4%) were enrolled in Italian centers and 2,626 (61.6%) in non-Italian centers. The Italian cohort was further stratified into Northern (52.9%), Central (25.7%), and Southern (21.4%) regions.

Baseline characteristics are summarized in Table 1 and Supplementary Tables 1A–C. Clinical profiles were broadly similar between cohorts. Most patients had a pre-test probability (PTP) $>15\%$ (68.3% vs. 68.0%), whereas only a minority had PTP $<5\%$ (4.5% vs. 5.9%). Previous CAD was present in 27.2% vs. 26.1% of patients, and reduced LVEF ($<50\%$) in 4.2% vs. 5.6% (Table 1). Compared with the non-Italian cohort, patients in Italy were older (64.8 ± 11.1 vs. 62.7 ± 11.3 years, $p < 0.001$), more frequently male (64.5% vs. 57.0%, $p < 0.001$), and had a lower prevalence of major cardiovascular risk factors, including diabetes (18.2% vs. 23.5%), and obesity (22.6% vs. 31.4%) but a higher prevalence of smoking (47.4% vs. 38.8%), (Table 1). Across both cohorts, the burden of risk factors increased with higher PTP and was greatest in patients with reduced LVEF and/or previous CAD. Medical therapy was generally less intensive in the Italian cohort, with lower use of beta-

blockers (43.8% vs. 50.1%), calcium channel blockers (16.7% vs. 25.5%), nitrates (2.3% vs. 10.6%), and diuretics (15.4% vs. 19.4%), while RAAS inhibitor use was similar (Supplementary Tables 2A–B). Atypical angina was more frequent in Italy (64.4% vs. 49.3%), whereas typical angina was less common (16.8% vs. 32.3%, $p<0.001$).

Within Italy, regional differences were observed: patients from Central Italy were older and had a higher prevalence of cardiovascular risk factors, along with a higher frequency of atypical symptom presentation (Supplementary Tables 1A–C).

Use of imaging tests and test results

The use and results of exercise ECG, coronary CT angiography (CTCA), stress imaging, and invasive coronary angiography (ICA) are summarized in Figure 1 and Supplementary Tables 4A–B. Compared with the non-Italian cohort, the Italian cohort showed a distinct pattern of test utilization. Exercise ECG was performed more frequently in Italy (39.6% vs. 25.5%), particularly in patients with low PTP (64.9% vs. 46.2% for $PTP \leq 5\%$ and 50.1% vs. 29.3% for $PTP 5\text{--}15\%$), but remained widely used even in higher-risk subgroups. Among non-invasive imaging modalities, CTCA was more frequently used in the Italian cohort (35.0% vs. 20.2%) and was also applied in patients with previous CAD (24.6% vs. 9.7% in those with preserved LVEF), unlike in the non-Italian cohort. In contrast, stress imaging was less frequently performed in Italy (39.4% vs. 45.9%), mainly due to lower use of SPECT (18.2% vs. 28.0%) and stress echocardiography (15.6% vs. 17.3%). Advanced techniques such as stress CMR (3.8% vs. 0.1%) and CT perfusion (1.8% vs. 0.2%) were more frequently used in Italy, although in a small proportion of patients. ICA was less frequently performed in Italy overall (22.9% vs. 34.5%) and much less often used as a first-line test (6.2% vs. 24.8%). Invasive functional assessment (FFR/iFR) was infrequently adopted in both cohorts (8.3% vs. 6.3% and 1.1% vs. 1.7%, respectively). The prevalence of high-risk findings was similar across most non-invasive modalities, although higher for CTCA in the Italian cohort (5.6% vs. 2.1%). Consistently, obstructive CAD at ICA was less frequently detected in Italy (11.9% vs. 15.7%). Across both cohorts, the use of imaging modalities and the prevalence of abnormal findings increased with higher PTP, reduced LVEF, and prior CAD.

Within Italy, marked regional differences were observed. Exercise ECG was most frequently used in Southern Italy (64% vs. 33% and 32.8% in Northern and Central regions), whereas CTCA use was highest in Northern Italy (46.7% vs. 28.3% and 14.0% in Central and Southern regions), particularly among patients with prior CAD. Stress imaging was more commonly used in Central Italy, while ICA was more frequently performed in Central regions (33% vs. 19.8% and 18.6%) and more often used as a first-line test in Southern Italy (12.6% vs. 3.4% and 6.7%).

Adoption of ESC guideline recommendations and effects on initial patient management

Results for guideline adoption are summarized in the Central Illustration. Compared with the non-Italian cohort, guideline adoption was higher in the Italian cohort, both for the initial diagnostic test (Endpoint A: 69.9% vs. 62.3%, $p<0.001$) and for the overall diagnostic pathway (Endpoint B: 62.1% vs. 57.0%, $p<0.001$). In both cohorts, adherence was highest in patients with intermediate PTP (5–15%) and lower in those with $PTP >15\%$ or reduced LVEF, particularly in patients with $LVEF <50\%$ and known CAD. Low adherence was also observed in patients with $PTP <5\%$, in whom no further testing is recommended.

Determinants of guideline adoption in the Italian cohort were consistent with those observed in the overall population (Figure 2). Integrated stress imaging was the strongest independent predictor of guideline-concordant management (adjusted OR 7.13, 95% CI 4.76–10.67; $p<0.001$), followed by female sex (adjusted OR 2.06, 95% CI 1.55–2.73; $p<0.01$). In contrast, invasive coronary angiography (adjusted OR 0.30, 95% CI 0.22–0.42; $p<0.001$) and exercise ECG (adjusted OR 0.27, 95% CI 0.18–0.40; $p=0.001$) were independently associated with lower adherence, while CTCA was not significantly associated (adjusted OR 1.34, 95% CI 0.86–2.09; $p=0.193$).

Within Italy, adoption rates for both Endpoint A and Endpoint B were lower in Southern regions compared with Central and Northern areas, with no significant regional differences in the determinants of adherence.

Adoption of ESC guideline recommendations and follow-up

Follow-up duration was similar in the Italian and non-Italian cohorts (median 185.5 [IQR 72] vs. 183 [IQR 56] days). During 6-month follow-up, MACE occurred less frequently in the Italian cohort (1.8% vs. 3.1%, $p=0.007$). However, MACE incidence did not differ according to guideline adoption in either cohort. Time to first MACE was longer in the Italian cohort ($p<0.001$), without significant differences according to guideline adherence. No significant differences were observed between cohorts for the composite endpoint of cardiac death and non-fatal myocardial infarction. All-cause death was rare but differed between groups (1 vs. 11 events, $p=0.036$), and hospitalizations for other cardiac causes were less frequent in the Italian cohort (15 vs. 66 events, $p<0.001$). Time to late coronary revascularization was longer in Italy (197 vs. 99 days, $p<0.001$), particularly in Central and Southern regions ($p=0.001$). Patients in the Italian cohort reported higher quality-of-life scores at baseline and at 6 months ($p<0.001$), and a greater proportion reported symptom improvement (72% vs. 59.6%, $p<0.001$). Improved symptoms were associated with guideline adherence in the non-Italian cohort ($p<0.05$), but not in the Italian cohort ($p=0.12$). The rate of additional imaging during follow-up was similar between cohorts (3.2% vs. 4.0%, $p=0.182$), although in the non-Italian cohort it was lower among patients managed according to guideline recommendations (3.3% vs. 5.0%, $p=0.036$).

Within Italy, MACE rates were similar across regions (Northern 1.9%, Central 2.6%, Southern 0.9%; $p=0.79$). However, time to MACE was shorter in Northern Italy (130 days) compared with Central (314 days) and Southern regions (256 days) ($p<0.001$), driven by earlier revascularization. Additional imaging during follow-up was more frequent in Central Italy (6.7%) than in Northern (2.1%) and Southern regions (2.0%).

DISCUSSION

Our results show that, despite slightly higher adherence in Italy compared with other countries, the implementation of ESC guideline recommendations for chronic coronary syndromes remains suboptimal in real-world practice. In the Italian cohort, stress imaging was less frequently used, while exercise ECG remained the most commonly performed test, despite its known limitations in diagnostic accuracy. Notably, exercise ECG was also used in patients with reduced LVEF, in whom invasive coronary angiography (ICA) would be more appropriate (19,20). Regarding anatomical strategies, ICA was less frequently performed in Italy, whereas CTCA was more commonly used as a first-line test, including in patients with intermediate or high PTP and in those with previous CAD. This pattern suggests a shift toward anatomical imaging approaches that may not always align with guideline-directed strategies. At the same time, the lower use of ICA was not consistently preceded by appropriate non-invasive imaging, and the use of invasive functional assessment remained limited in both cohorts. Overall, referral to exercise ECG and direct use of ICA as initial diagnostic tests emerged as the main drivers of non-adherence to guideline recommendations in both cohorts. Finally, major adverse cardiovascular events at 6 months were infrequent and not associated with guideline adherence, likely reflecting the relatively low-risk profile of the study population and the short follow-up duration.

Population characteristics and management

A high prevalence of hypertension and dyslipidemia was observed in both cohorts, whereas obesity was less common in the Italian population, possibly reflecting differences in lifestyle patterns. Atypical angina or chest pain equivalents represented the most frequent clinical presentation in Italy. Most patients had no previous CAD and a moderate-to-high pre-test probability, with guideline adherence highest in the intermediate PTP category.

The prevalence of obstructive CAD was lower in the Italian cohort compared with the non-Italian cohort (19.9% vs. 26.9%), despite similar rates of revascularization, likely driven by comparable rates of inducible ischemia. These findings are consistent with previous imaging studies (3–11) and with the progressive downgrading of pre-test probability estimates in the 2019 ESC guidelines (1) and the 2024 update (12). Conversely, non-obstructive CAD was more prevalent in the Italian cohort, while modifications of medical therapy were less frequent. This pattern may represent an emerging clinical challenge, as non-obstructive CAD is increasingly recognized but not adequately captured by traditional pre-test probability models.

Within Italy, the lower prevalence of obstructive CAD and inducible ischemia, together with lower rates of revascularization and treatment changes in Southern regions, highlights substantial geographic disparities. These differences likely reflect variability in access to imaging technologies and healthcare organization, with potential implications for clinical decision-making and patient outcomes (13).

Use of imaging test

Compared with the non-Italian cohort, the Italian cohort showed a greater use of exercise ECG—particularly in Southern regions—and of CT coronary angiography (CTCA), especially in Northern Italy. In contrast, stress imaging and ICA were less frequently performed, and invasive functional assessment (FFR/iFR) was used in only a minority of patients in both cohorts. This pattern of imaging utilization likely reflects multiple contributing factors. The increasing use of CTCA, particularly in patients with intermediate or high PTP, may be in line with more recent recommendations (21,22) and facilitated by greater availability of CT technology, especially in Northern regions. Conversely, the persistent reliance on exercise ECG in Southern Italy may reflect historical practice patterns or overestimation of its diagnostic performance. Importantly, the limited use of stress imaging and invasive functional assessment, despite strong guideline recommendations, suggests the presence of structural and organizational barriers. These may include long waiting times, limited availability of advanced imaging modalities, and differences in reimbursement policies, as well as local interventional practice patterns.

Adoption of ESC guideline recommendations and effects on initial patient management

Guideline recommendations for the management of CCS were more frequently adopted in the Italian cohort. In both cohorts, patients managed according to guideline recommendations were less often evaluated in cardiology or university centers, suggesting that non-adoption was not primarily driven by limited access to multimodality imaging. Patients managed in accordance with guidelines were more frequently referred to stress imaging or CTCA, whereas direct referral to ICA as the first diagnostic test emerged as a major driver of non-adherence. Barriers to guideline implementation likely include local practice patterns, variable availability of imaging modalities, financial and reimbursement factors, as well as healthcare system organization.

Overall, our findings confirm a persistent gap between guideline-recommended strategies and real-world clinical practice in both Italian and non-Italian settings. The assumption that early identification of obstructive CAD by ICA, followed by immediate revascularization, improves outcomes has not been supported by randomized clinical trials (14–16). On the contrary, this approach may contribute to a lower diagnostic yield of ICA (17) and a reduced proportion of procedures leading to revascularization when performed outside guideline-directed pathways.

Adoption of ESC guideline recommendations and follow-up

The lack of association between guideline adherence and short-term clinical outcomes likely reflects the low-risk profile of the study population and the relatively short follow-up duration, rather than the absence of clinical benefit from guideline-directed strategies. Nevertheless, potential differences in outcomes cannot be excluded with longer-term follow-up. In the non-Italian cohort, guideline adoption was associated with greater symptomatic improvement, despite similar rates of additional diagnostic testing. In contrast, this association was not observed in the Italian cohort. Notably, baseline VAS scores were higher in the Italian cohort, suggesting less room for

improvement. Whether the more frequent changes in medical therapy observed in the non-Italian cohort contributed to the greater symptomatic benefit remains to be established.

Limitations

As an international registry, several limitations should be acknowledged. A substantial proportion of participating centers were academic tertiary referral institutions, which may limit the generalizability of the findings to routine clinical practice. In addition, the heterogeneity of healthcare systems across countries, including differences in costs, reimbursement policies, and organizational factors, may have influenced diagnostic pathways. The choice of diagnostic strategies—such as the use of ICA without prior non-invasive imaging—may also have been affected by local practice patterns, resource availability, and physician or patient preferences. Furthermore, the COVID-19 pandemic may have impacted the use of imaging modalities and waiting times during the study period. In addition, although only small differences on symptoms and smoking habits were found between the included and excluded patients, we cannot completely exclude that it may represent a potential selection bias. Finally, the potential impact of the most recent guideline updates on clinical practice remains to be determined (24).

Clinical implication

Among the Italian and non-Italian cohorts of the EURECA registry, a large proportion of patients with CCS do not follow the diagnostic pathways recommended by the 2019 ESC Guidelines based on a pre-test probability strategy. The proliferation of non-invasive tests for CCS increases healthcare costs, and the rationale for widespread screening for CCS is questioned given the declining prevalence of obstructive CAD (1,12), as confirmed in the EURECA registry, and the lack of evidence for a prognostic benefit of revascularization in the ISCHEMIA trial (24). The shift from invasive to non-invasive imaging is likely to transform CCS management in the coming years, enabling more precise diagnostic and prognostic stratification and supporting personalized therapies. In this perspective, non-obstructive CAD represents the most frequent phenotype in both cohorts, highlighting the need for dedicated large-scale studies to better define optimal diagnostic and management strategies beyond traditional risk-based approaches (25). The potential benefits of appropriate diagnostic pathways may not be apparent at 6 months and may become evident during the ongoing 3-year follow-up.

CONCLUSIONS

Although guideline adherence was higher in Italy than in other countries, a substantial gap between recommendations and clinical practice persists. This gap is largely driven by the frequent use of exercise ECG and the direct referral of a significant proportion of patients to invasive coronary angiography without prior non-invasive stress imaging in both cohorts. Within Italy, this discrepancy is more pronounced in Southern regions.

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Central Illustration: Adoption of the 2019 ESC Guidelines for Chronic Coronary Syndromes: initial diagnostic testing (Endpoint A), overall diagnostic pathway (Endpoint B) and regional variability in the Italian cohort.

Panel A. Adoption of Guidelines by cohort (Italian vs. non-Italian) and subcohort (Northern, Central, and Southern Italy).

Panel B. Adoption of Guidelines by cohort (Italian vs. non-Italian) according to previous coronary artery disease (CAD) and pre-test probability (PTP).

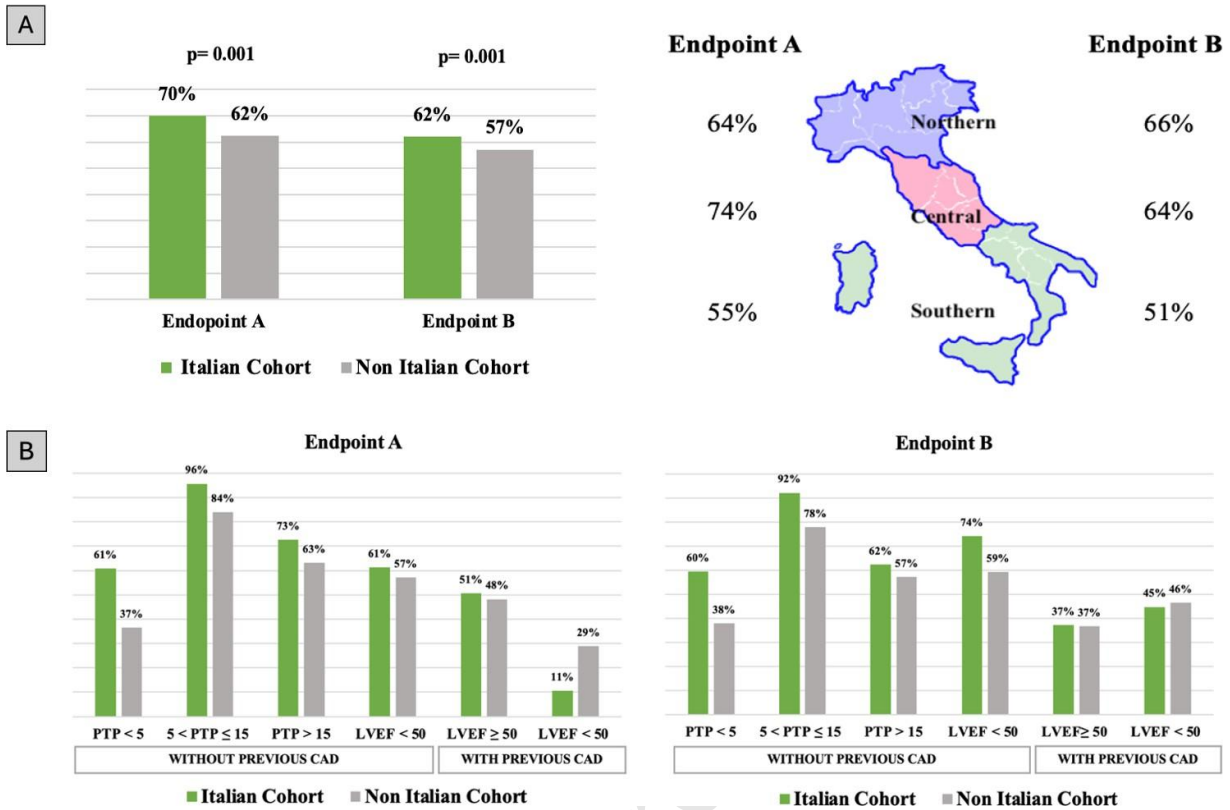
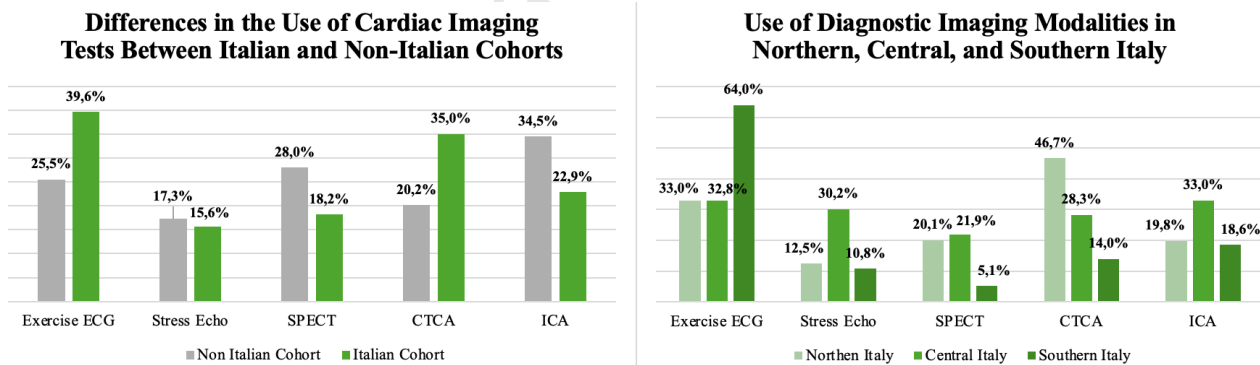


Figure 1. Differences in Use of Cardiac Imaging. 1A. Differences in the Use of Cardiac Imaging Tests Between Italian and Non-Italian Cohorts. 1B. Use of Diagnostic Imaging Modalities in Northern, Central, and Southern Italy.



CTCA: computed tomography coronary angiography; ICA: invasive coronary angiography; SPECT: Single Photon Emission Computed Tomography.

Figure 2. Independent predictors of adherence to the 2019 ESC guidelines.

Adjusted OR (95% CI)

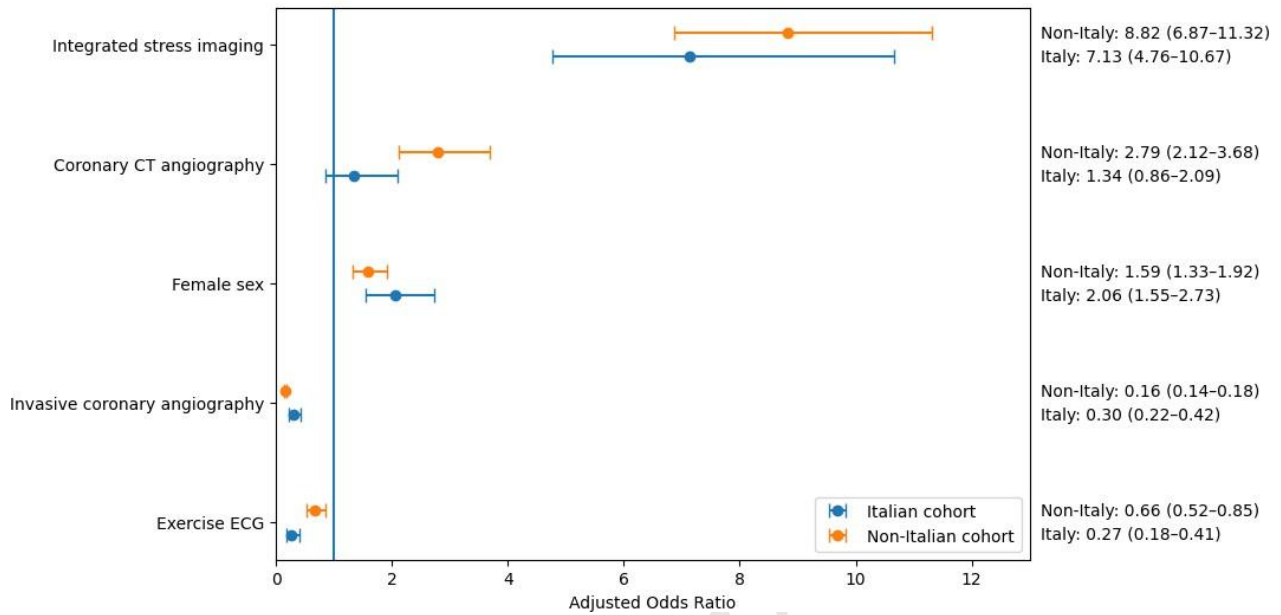


Table 1. Baseline patient characteristics of Italian cohort compared to non Italian cohort.

Table 1	ITALIAN COHORT									NON ITALIAN COHORT									P-VALUE
	TOTAL N=1,636 (38.4%)	P-VALUE	PATIENTS WITHOUT PREVIOUS CAD				P-VALUE	PATIENTS WITH PREVIOUS CAD		TOTAL N=2,626 (61.6%)	P-VALUE	PATIENTS WITHOUT PREVIOUS CAD				P-VALUE	PATIENTS WITH PREVIOUS CAD		
			PTP < 5% (N=74)	5 < PTP ≤ 15 (N=347)	PTP > 15 (N=740)	LVEF < 50 (N=31)		LVEF ≥ 50 (N=406)	LVEF < 50 (N=38)			PTP < 5% (N=156)	5 < PTP ≤ 15 (N=677)	PTP > 15 (N=1,060)	LVEF < 50 (N=49)		LVEF ≥ 50 (N=587)	LVEF < 50 (N=97)	
Age (mean, SD)	64.8 (11.1)	<0.001	42.9 (10.3)	57.6 (8.9)	68.3 (9.0)	70.4 (11.9)	0.932	67.8 (9.1)	68.0 (9.0)	62.7 (11.3)	<0.001	42.8 (8.8)	57.8 (9.5)	66.6 (9.2)	68.4 (9.8)	0.986	65.9 (9.9)	65.9 (10)	<0.001
Male Gender	1,055 (64.5%)	<0.001	35 (47.3%)	77 (22.2%)	547 (73.9%)	22 (71%)	0.997	342 (84.2%)	32 (84.2%)	1,497 (57.0%)	<0.001	74 (47.4%)	128 (18.9%)	741 (69.9%)	32 (65.3%)	0.01	438 (74.6%)	84 (86.6%)	<0.001
BMI (mean, SD), missing=308	26.9 (4.4)	0.001	25.9 (5.1)	26.1 (4.3)	27.2 (4.3)	27.4 (4.5)	0.892	27.4 (4.2)	27.5 (3.9)	28.3 (4.9)	0.006	27.2 (5.0)	28.6 (5.4)	28.2 (4.7)	29.2 (4.7)	0.877	28.5 (4.5)	28.6 (4.7)	<0.001
Typical Angina Presentation	275 (16.8%)	<0.001	1 (1.4%)	22 (6.3%)	156 (21.1%)	5 (16.1%)	0.208	79 (19.5%)	12 (31.6%)	847 (32.3%)	<0.001	8 (5.1%)	83 (12.3%)	464 (43.8%)	7 (14.3%)	0.366	241 (41.1%)	44 (45.4%)	<0.001
Atypical Anting Presentation	1,053 (64.4%)		26 (35.1%)	254 (73.2%)	483 (65.3%)	21 (67.7%)		249 (61.3%)	20 (52.6%)	1,294 (49.3%)		37 (23.7%)	405 (59.8%)	501 (47.3%)	29 (59.2%)		276 (47.0%)	46 (47.4%)	
Non anginal pain presentation	308 (18.8%)		47 (63.5%)	71 (20.5%)	101 (13.7%)	5 (16.1%)		78 (19.2%)	6 (15.8%)	484 (18.4%)		111 (71.2%)	189 (27.9%)	94 (8.9%)	13 (26.5%)		70 (11.9%)	7 (7.2%)	
Family history, missing=412	602 (38.8%)	0.092	25 (35.2%)	144 (43%)	243 (34.9%)	11 (37.9%)	0.013	171 (44.5%)	8 (22.9%)	853 (37.1%)	0.053	57 (40.1%)	246 (40.4%)	312 (33.8%)	15 (38.5%)	0.987	192 (38.1%)	31 (37.4%)	0.272
Smoking, missing=103	763 (47.4%)	0.002	25 (33.8%)	126 (36.7%)	334 (45.9%)	19 (61.3%)	0.747	236 (59.5%)	23 (62.2%)	989 (38.8%)	0.019	52 (33.8%)	196 (30.0%)	377 (36.8%)	21 (42.9%)	0.004	282 (49.0%)	61 (64.9%)	<0.001
Diabetes mellitus, missing=24	297 (18.2%)	<0.001	2 (2.7%)	40 (11.6%)	147 (19.9%)	9 (30.0%)	0.311	88 (21.8%)	11 (29.0%)	614 (23.5%)	0.001	13 (8.4%)	143 (21.3%)	230 (21.8%)	7 (14.3%)	0.378	186 (31.9%)	35 (36.5%)	<0.001
Dyslipidemia, missing=74	987 (60.7%)	<0.001	18 (24.7%)	160 (46.4%)	429 (58.3%)	16 (53.3%)	0.655	331 (81.9%)	33 (86.8%)	1,676 (65.4%)	<0.001	49 (32.0%)	374 (56.8%)	664 (64.5%)	27 (55.1%)	0.831	481 (83.5%)	81 (84.4%)	0.002

Hypertension, missing=31	1,127 (69.2%)	<0.001	17 (23.3%)	182 (52.8%)	535 (72.6%)	27 (87.1%)	0.834	335 (82.9%)	31 (81.6%)	1,790 (68.8%)	<0.001	56 (35.9%)	394 (58.5%)	748 (71.5%)	34 (69.4%)	0.713	477 (82.0%)	81 (83.5%)	0.753
Obesity, missing=57	340 (20.9%)	0.074	13 (17.8%)	56 (16.3%)	165 (22.3%)	9 (29.0%)	0.739	88 (22.0%)	9 (24.3%)	810 (31.4%)	0.011	28 (18.2%)	206 (31.2%)	321 (30.8%)	15 (31.3%)	0.431	209 (36.1%)	31 (32.0%)	<0.001
Prior myocardial infarction, missing=65	275 (17.2%)	-	-	-	-	-	<0.001	241 (61.5%)	34 (91.9%)	449 (17.3%)	-	-	-	-	-	<0.001	363 (62.8%)	86 (92.5%)	0.921
LVEF (%), missing=2,002	56.8 (6.8)	<0.001	60.6 (2.9)	59.3 (4.1)	58.7 (4.6)	41.9 (4.9)	<0.001	56.8 (5.1)	41.4 (5.8)	59.0 (8.4)	<0.001	63.4 (5.9)	61 (5.5)	61.3 (5.3)	41 (5.9)	<0.001	59.2 (5.9)	40.3 (6.6)	<0.001
Previous revascularization, missing=6	413 (25.2%)	-	-	-	-	-	0.026	381 (93.8%)	32 (84.2%)	584 (22.3%)	-	-	-	-	-	0.985	501 (85.5%)	83 (85.6%)	0.027
PCI	373 (22.8%)	-	-	-	-	-	0.101	345 (85.0%)	28 (73.7%)	500 (19.1%)	-	-	-	-	-	0.215	434 (76.1%)	66 (68.0%)	0.003
CABG	76 (4.7%)	-	-	-	-	-	0.261	67 (16.5%)	9 (23.7%)	130 (5.0%)	-	-	-	-	-	0.27	101 (17.2%)	29 (29.9%)	0.64

Table 2. Final clinical diagnosis and early management

Table 2	ITALIAN COHORT								NON ITALIAN COHORT								P-VALUE		
	TOT AL N=1,636 (38.4%)	P-VALUE	PATIENTS WITHOUT PREVIOUS CAD				P-VALUE	PATIENTS WITH PREVIOUS CAD		TOT AL N=2,626 (61.6%)	P-VALUE	PATIENTS WITHOUT PREVIOUS CAD				P-VALUE		PATIENTS WITH PREVIOUS CAD	
			PTP < 5% (N=74)	5 < PTP ≤ 15 (N=347)	PTP > 15 (N=740)	LVE F < 50 (N=31)		LVE F ≥ 50 (N=406)	LVE F < 50 (N=38)			PTP < 5% (N=156)	5 < PTP ≤ 15 (N=677)	PTP > 15 (N=1,060)	LVE F < 50 (N=49)			LVE F ≥ 50 (N=587)	LVE F < 50 (N=97)
Obstructive CAD	303 (19.9%)	<0.001	0	14 (4.3%)	151 (22.0%)	11 (37.9%)	0.117	111 (29.8%)	16 (47.1%)	641 (26.9%)	<0.001	5 (3.7%)	59 (9.8%)	267 (27.6%)	15 (34.9%)	0.085	248 (45.2%)	47 (52.8%)	<0.001
Non obstructive CAD	706 (46.4%)		31 (44.3%)	132 (40.4%)	295 (42.9%)	11 (37.9%)		222 (59.5%)	15 (44.1%)	786 (32.9%)		23 (17.2%)	175 (29.0%)	311 (32.1%)	12 (27.9%)		228 (41.5%)	37 (41.6%)	
No CAD	512 (33.7%)		39 (55.7%)	181 (55.4%)	242 (35.2%)	7 (24.1%)		40 (10.7%)	3 (8.8%)	959 (40.2%)		106 (79.1%)	369 (61.2%)	390 (40.3%)	16 (37.2%)		73 (13.3%)	5 (5.6%)	
Inducible ischemia	281 (19.3%)	<0.001	3 (4.6%)	30 (9.7%)	121 (18.9%)	10 (43.5%)	0.13	103 (27%)	14 (38.9%)	453 (18.9%)	<0.001	7 (5.1%)	75 (12.4%)	181 (18.6%)	9 (20.5%)	0.034	146 (27%)	35 (38%)	0.74
No iducible Ischemia	1,172 (80.7%)		63 (95.5%)	278 (90.3%)	518 (81.1%)	13 (56.5%)		278 (73%)	22 (61.1%)	1,943 (81.1%)		130 (94.9%)	532 (87.6%)	795 (81.5%)	35 (79.6%)		394 (73%)	57 (62%)	
Revascularization	210 (12.8%)	<0.001	0	11 (3.2%)	115 (15.5%)	6 (19.4%)	0.018	66 (16.3%)	12 (31.6%)	368 (14%)	<0.001	3 (1.9%)	32 (4.7%)	172 (16.2%)	5 (10.2%)	0.785	133 (22.7%)	23 (24%)	0.271
No Revascularization	1426 (87.2%)		74 (100%)	336 (96.8%)	625 (84.5%)	25 (80.7%)		340 (83.7%)	26 (68.4%)	2256 (86%)		153 (98.1%)	645 (95.3%)	888 (83.8%)	44 (89.8%)		453 (77.3%)	73 (76%)	
Change/New treatment	537 (33.1%)	<0.001	10 (13.5%)	84 (24.5%)	273 (37.4%)	18 (58.1%)	0.122	135 (33.3%)	17 (46%)	1022 (40.4%)	<0.001	24 (16.6%)	213 (32.9%)	454 (44.3%)	29 (59.2%)	0.391	255 (44.7%)	47 (49.5%)	<0.001
No Change/new treatment	1084 (66.9%)		64 (86.5%)	259 (75.5%)	458 (62.7%)	13 (41.9%)		270 (66.7%)	20 (54.1%)	1510 (59.6%)		121 (83.5%)	435 (67.1%)	571 (55.7%)	20 (40.8%)		315 (55.3%)	48 (50.5%)	

SUPPLEMENTARY MATERIAL

Table 1A. Patient characteristics in the Northern Italy cohort

TABLE 1 A	NORTHERN ITALY
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	TOTAL N=865 (52.9%)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENTS WITH PREVIOUS CAD	
			PTP < 5% (N=33)	5 < PTP ≤ 15 (N=172)	PTP > 15 (N=391)	LVEF < 50% (N=15)		LVEF ≥ 50 (N=232)	LVEF < 50 (N=22)
AGE (MEAN, SD)	64.7 (11.0)	<0.001	44.1 (10.8)	56.8 (9.0)	68.3 (9.2)	68.8 (12.7)	0.267	67.1 (9.2)	64.8 (8.0)
MALE GENDER	561 (64.9%)	<0.001	13 (39.4%)	42 (24.4%)	288 (73.7%)	10 (66.7%)	0.556	191 (82.3%)	17 (77.3%)
BMI (MEAN, SD), MISSING=308	26.7 (4.5)	0.001	24.8 (4.2)	25.6 (4.4)	27.1 (4.5)	27.3 (5.0)	0.657	27.1 (4.2)	26.7 (3.6)
SYMPTOMS (TYPICAL, ATYPICAL, NON-ANGINAL), MISSING=1									
- TYPICAL	157 (18.2%)	<0.001	0	18 (10.5%)	91 (23.3%)	2 (13.3%)	0.197	39 (16.8%)	7 (31.8%)
- ATYPICAL	558 (64.5%)		12 (36.4%)	122 (70.9%)	253 (64.7%)	9 (60%)		151 (65.1%)	11 (50.0%)
- NON ANGINAL	150 (17.359)		21 (63.6%)	32 (18.6%)	47 (12.0%)	4 (26.7%)		42 (18.1%)	4 (18.2%)
FAMILY HISTORY, MISSING=412	396 (47.8%)	0.369	13 (39.4%)	85 (50.9%)	161 (43.4%)	6 (42.9%)	0.027	125 (55.8%)	6 (30%)
SMOKING, MISSING=103	422 (49.7%)	0.002	10 (30.3%)	59 (34.9%)	187 (48.8%)	10 (66.7%)	1	143 (62.5%)	13 (61.9%)
DIABETES MELLITUS, MISSING=24	145 (16.8%)	0.001	1 (3%)	19 (11.1%)	68 (17.5%)	7 (46.7%)	0.400	44 (19.1%)	6 (27.3%)
DYSLIPIDEMIA, MISSING=74	511 (59.6%)	0.006	10 (31.3%)	76 (44.4%)	219 (56.4%)	7 (50%)	0.429	180 (77.9%)	19 (86.4%)
HYPERTENSION, MISSING=31	572 (66.5%)	<0.001	5 (15.6%)	81 (47.4%)	278 (71.5%)	13 (86.7%)	0.791	177 (76.6%)	18 (81.8%)
OBESITY, MISSING=57	164 (19.1%)	0.440	5 (15.6%)	27 (15.8%)	80 (20.5%)	4 (26.7%)	1	44 (19.1%)	4 (19.1%)
PRIOR MYOCARDIAL INFARCTION, MISSING=65	136 (16.2%)	-	-	-	-	-	<0.001	116 (52.3%)	20 (95.2%)
LVEF (%), MISSING=2,002	56.7 (7.7)	<0.001	60.7 (3.1)	59.8 (4.9)	59.3 (4.5)	42.5 (4.6)	<0.001	57.8 (4.9)	39.8 (6.3)
PREVIOUS REVASCULARIZATION, MISSING=6	245 (28.3%)	-	-	-	-	-	0.034	226 (97.4%)	19 (86.4%)
- PCI	225 (26%)	-	-	-	-	-	0.026	209 (90.1%)	16 (72.7%)
- CABG	45 (5.2%)	-	-	-	-	-	0.242	39 (16.8%)	6 (27.3%)

Table 1B. Patient characteristics in the Central Italy cohort

TABLE 1B	CENTRAL ITALY								
	TOTAL N=421 (25.7%)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENTS WITH PREVIOUS CAD	
			PTP < 5% (N=10)	5 < PTP ≤ 15 (N=90)	PTP > 15 (N=201)	LVEF <50% (N=9)		LVEF ≥ 50 (N=103)	LVEF < 50 (N=8)
AGE (MEAN, SD)	66.6 (10.5)	<0.001	42.2 (8.4)	58.6 (8.8)	69.1 (8.7)	76.7 (7.6)	0.788	69.8 (8.5)	70.6 (8.7)
MALE GENDER	260 (61.8%)	<0.001	4 (40%)	14 (15.6%)	141 (70.2%)	5 (55.6%)	0.595	88 (85.4%)	8 (100%)
BMI (MEAN, SD), MISSING=308	27.5 (4.3)	0.919	27.2 (7.9)	27.0 (4.4)	27.4 (4.2)	27.5 (3.5)	0.861	28.2 (4.0)	28.4 (2.7)
SYMPTOMS (TYPICAL, ATYPICAL, NON-ANGINAL), MISSING=1									
- TYPICAL	78 (18.5%)	<0.001	1 (10%)	2 (2.2%)	39 (19.4%)	1 (11.1%)	0.064	31 (30.1%)	4 (50%)
- ATYPICAL	311 (73.9%)		3 (30%)	76 (84.4%)	151 (75.1%)	8 (88.9%)		70 (68%)	3 (37.5%)
- NON ANGINAL	32 (7.6%)		6 (60%)	12 (13.3%)	11 (5.5%)	0		2 (1.9%)	1 (12.5%)
FAMILY HISTORY, MISSING=412	107 (26%)	0.493	3 (30%)	27 (30%)	45 (23.1%)	3 (33.3%)	0.443	28 (28.3%)	1 (12.5%)
SMOKING, MISSING=103	196 (47.1%)	0.267	5 (50%)	33 (36.7%)	89 (44.7%)	6 (66.7%)	1	58 (58%)	5 (62.5%)
DIABETES MELLITUS, MISSING=24	86 (20.5%)	0.091	0	11 (12.2%)	44 (21.9%)	1 (11.1%)	0.681	27 (26.5%)	3 (37.5%)
DYSLIPIDEMIA, MISSING=74	266 (63.2%)	0.003	2 (20%)	40 (44.4%)	126 (62.7%)	5 (55.6%)	0.614	87 (84.5%)	6 (75%)
HYPERTENSION, MISSING=31	306 (72.7%)	<0.001	1 (10%)	51 (56.7%)	145 (72.1%)	9 (100%)	0.18	94 (91.3%)	6 (75%)
OBESITY, MISSING=57	98 (23.3%)	0.485	2 (20%)	13 (14.6%)	45 (22.4%)	2 (22.2%)	1	34 (33%)	2 (25%)
PRIOR MYOCARDIAL INFARCTION, MISSING=65	70 (16.7%)	-	-	-	-	-	0.254	63 (61.8%)	7 (87.5%)
LVEF (%), MISSING=2,002	57.3 (5.8)	<0.001	60 (3.9)	59.6 (3.9)	58.5 (4.7)	42.9 (3.9)	<0.001	56 (4.7)	43.5 (5.6)
PREVIOUS	103	-	-	-	-	-	0.462	96 (93.2%)	7 (87.5%)

REVASCULARIZATION, MISSING=6	(24.5%)								
- PCI	95 (22.6%)	-	-	-	-	-	0.324	89 (86.4%)	6 (75%)
- CABG	11 (2.6%)	-	-	-	-	-	0.18	9 (8.7%)	2 (25%)

Table 1C. Patient characteristics in the Southern Italy cohort

TABLE 1C	SOUTHERN ITALY								
	TOTAL N=350 (21.4%)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENTS WITH PREVIOUS CAD	
			PTP < 5% (N= 31)	5 < PTP ≤ 15 (N= 85)	PTP > 15 (N= 148)	LVEF <50% (N=7)		LVEF ≥ 50 (N=71)	LVEF < 50 (N=8)
AGE (MEAN, SD)	63.0 (11.9)	<0.001	41.8 (10.4)	58.2 (8.7)	67.3 (13.0)	65.9 (9.3)	0.064	67.5 (9.3)	74.0 (8.8)
MALE GENDER	234 (66.9%)	<0.001	18 (58.1%)	21 (24.7%)	118 (79.7%)	7 (100%)	1	63 (88.7%)	7 (87.5%)
BMI (MEAN, SD), MISSING=308	26.8 (4.1)	0.459	26.6 (4.9)	26.2 (3.9)	27.0 (3.9)	27.5 (4.8)	0.41	27.0 (4.4)	28.4 (5.5)
SYMPTOMS (TYPICAL, ATYPICAL, NON-ANGINAL), MISSING=1									
- TYPICAL	40 (11.4%)	<0.001	0	2 (2.4%)	26 (17.6%)	2 (28.6%)	0.121	9 (12.7%)	1 (12.5%)
- ATYPICAL	184 (52.6%)		11 (35.5%)	56 (65.9%)	79 (53.4%)	4 (57.1%)		28 (39.4%)	6 (75%)
- NON ANGINAL	126 (36.0%)		20 (64.5%)	27 (31.8%)	43 (29.1%)	1 (14.3%)		34 (47.9%)	1 (12.5%)
FAMILY HISTORY, MISSING=412	99 (31.9%)	0.317	9 (32.1%)	32 (41%)	37 (28.5%)	2 (33.3%)	0.664	18 (29.5%)	1 (14.3%)
SMOKING, MISSING=103	145 (42.3%)	0.853	10 (32.3%)	34 (40.5%)	58 (40%)	3 (42.9%)	0.715	35 (51.5%)	5 (62.5%)
DIABETES MELLITUS, MISSING=24	66 (19%)	0.012	1 (3.2%)	10 (11.9%)	35 (23.7%)	1 (16.7%)	1	17 (23.9%)	2 (25%)
DYSLIPIDEMIA, MISSING=74	210 (60.5%)	0.001	6 (19.4%)	44 (52.4%)	84 (57.1%)	4 (57.1%)	1	84 (91.4%)	8 (100%)
HYPERTENSION, MISSING=31	249 (71.8%)	<0.001	11 (35.5%)	50 (59.5%)	112 (76.2%)	5 (71.4%)	<0.001	64 (91.4%)	7 (87.5%)
OBESITY, MISSING=57	78 (22.6%)	0.297	6 (20%)	16 (19.1%)	40 (27%)	3 (42.9%)	0.132	10 (14.7%)	3 (37.5%)
PRIOR MYOCARDIAL INFARCTION, MISSING=65	69 (20.4%)	-	-	-	-	-	0.557	62 (91.2%)	7 (87.5%)
LVEF (%), MISSING=2,002	56.1 (6.5)	<0.001	60.8 (2.1)	58.3 (3.7)	57.6 (3.7)	39.4 (6.2)	<0.001	56.3 (5.8)	43.6 (3.2)
PREVIOUS REVASCULARIZATION, MISSING=6	65 (18.6%)	-	-	-	-	-	0.626	59 (83.1%)	6 (75%)
- PCI	53 (15.1%)	-	-	-	-	-	1	47 (66.2%)	6 (75%)
- CABG	20 (5.7%)	-	-	-	-	-	0.672	19 (26.8%)	1 (12.5%)

Table 2A. Medical therapy in the Italian vs non-Italian cohorts

TABLE 2A	ITALIAN COHORT									NON-ITALIAN COHORT									P- V A L U E
	TO TA L N=1 ,636 (38. 4%)	P- V A L U E	PATIENTS WITHOUT PREVIOUS CAD				P- V A L U E	PATIENTS WITH PREVIOUS CAD		TO TA L N=2 ,626 (61. 6%)	P- V A L U E	PATIENTS WITHOUT PREVIOUS CAD				P- V A L U E	PATIENTS WITH PREVIOUS CAD		
			PT P < 5% (N= 74)	5 < PT P ≤ 15 (N= 347)	PT P > 15 (N= 740)	LV EF < 50 (N= 31)		LV EF ≥ 50 (N= 406)	LV EF < 50 (N= 38)			PT P < 5% (N= 156)	5 < PT P ≤ 15 (N= 677)	PTP > 15 (N=1 ,060)	LV EF < 50 (N= 49)		LV EF ≥ 50 (N= 587)	LV EF < 50 (N= 97)	
SAPT (ASPIRIN/AN TIPLATELET)	693 (42.8%)	<0.001	3 (4.1%)	61 (17.8%)	260 (35.6%)	16 (51.6%)	0.120	327 (80.9%)	26 (70.3%)	1,238 (47.8%)	<0.001	16 (10.3%)	213 (32.0%)	459 (44.1%)	19 (38.8%)	0.538	458 (78.8%)	73 (76.0%)	0.001
DAPT	99 (6.1%)	0.067	0	1 (0.3%)	14 (1.9%)	1 (3.2%)	0.004	69 (17.1%)	14 (37.8%)	155 (60.6%)	0.035	0	7 (1.1%)	23 (2.2%)	2 (4.1%)	0.656	104 (17.9%)	19 (19.8%)	0.868
ANTICOAGU LANTS	117 (7.2%)	<0.001	1 (1.4%)	12 (3.5%)	60 (8.2%)	6 (19.4%)	0.351	33 (8.2%)	5 (13.5%)	251 (9.7%)	<0.001	3 (1.9%)	40 (6.0%)	121 (11.6%)	17 (34.7%)	0.266	57 (9.8%)	13 (13.5%)	0.006

BETA-BLOCKERS	709 (43.8%)	<0.001	8 (10.8%)	92 (26.8%)	253 (34.7%)	21 (67.7%)	1	307 (76.0%)	28 (75.7%)	1,296 (50.1%)	<0.001	22 (14.2%)	267 (40.1%)	456 (43.8%)	31 (63.3%)	<0.001	429 (73.8%)	91 (94.8%)	<0.001
CALCIUM-ANTAGONISTS	270 (16.7%)	<0.001	2 (2.7%)	36 (10.5%)	138 (18.9%)	2 (6.5%)	0.297	87 (21.5%)	5 (13.5%)	660 (25.5%)	<0.001	15 (9.7%)	138 (20.7%)	289 (27.8%)	11 (22.5%)	0.046	186 (32.0%)	21 (21.9%)	<0.001
ANTI-ARRHYTHMICS	76 (4.7%)	0.128	0	18 (5.3%)	42 (5.8%)	1 (3.2%)	1	14 (3.5%)	1 (2.7%)	76 (2.9%)	0.092	1 (0.7%)	16 (2.4%)	34 (3.3%)	3 (6.1%)	0.016	15 (2.6%)	7 (7.3%)	0.003
NITRATES	37 (2.3%)	0.718	0	3 (0.9%)	11 (1.5%)	0	0.428	20 (5.0%)	3 (8.1%)	275 (10.6%)	0.001	2 (1.3%)	34 (5.1%)	92 (8.8%)	4 (8.2%)	0.315	119 (20.5%)	24 (25.0%)	<0.001
ACE INHIBITORS	556 (34.3%)	<0.001	3 (4.1%)	68 (19.8%)	241 (33.0%)	20 (64.5%)	0.733	204 (50.5%)	20 (54.1%)	889 (34.4%)	<0.001	16 (10.3%)	177 (26.6%)	332 (31.9%)	20 (4.8%)	0.004	282 (48.5%)	62 (64.6%)	0.995
ARBs	307 (19.0%)	<0.001	7 (9.5%)	46 (13.4%)	170 (23.3%)	5 (16.1%)	0.868	72 (17.8%)	7 (18.9%)	582 (22.5%)	<0.001	12 (7.7%)	134 (20.1%)	245 (23.5%)	12 (24.5%)	0.552	156 (26.9%)	23 (24.0%)	0.006
DIURETICS	250 (15.4%)	<0.001	4 (5.4%)	28 (8.2%)	132 (18.1%)	7 (22.6%)	0.001	65 (16.1%)	14 (37.8%)	503 (19.4%)	<0.001	7 (4.5%)	108 (16.2%)	212 (20.4%)	19 (38.8%)	0.011	125 (21.5%)	32 (33.3%)	0.001
RANOLAZINE	40 (2.5%)	0.812	0	1 (0.35)	5 (0.7%)	0	0.513	30 (7.4%)	4 (10.8%)	56 (2.2%)	0.131	0	5 (0.8%)	17 (1.6%)	1 (2.0%)	0.800	28 (4.8%)	5 (5.2%)	0.517

Table 2B. Medical therapy in Northern, Central, and Southern Italy

	NORTHERN ITALY								CENTRAL ITALY								SOUTHERN ITALY													
	TOT AL (N=8 65)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENT S WITH PREVIOUS S CAD	TOT AL (N=4 21)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENT S WITH PREVIOUS S CAD	TOT AL (N=3 50)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENT S WITH PREVIOUS S CAD						
			PTP < 5% (N=33)	5 < PTP ≤ 15 (N=172)	PTP > 15 (N=391)	LV EF <50 (N=15)					LVE F ≥ 50 (N=232)	LV EF < 50 (N=22)	PT P < 5% (N=10)	5 < PTP ≤ 15 (N=90)					PTP > 15 (N=201)	LV EF <50 (N=9)	LVE F ≥ 50 (N=103)	LV EF < 50 (N=8)			PTP < 5% (N=31)	5 < PTP ≤ 15 (N=85)	PTP > 15 (N=148)	LV EF <50 (N=7)	LVE F ≥ 50 (N=71)	LV EF < 50 (N=8)
SAPT (ASPIRIN/ANTI PLATELET)	371 (43.2 %)	<0.001	0	29 (17 %)	132 (34.2 %)	8 (53.3 %)	0.784	185 (79.7 %)	17 (77.3 %)	188 (45 %)	<0.001	0	16 (17.8 %)	74 (37 %)	6 (66.7 %)	0.108	87 (86.1 %)	5 (62.5 %)	134 (39.2 %)	0.002	3 (9.7 %)	16 (19.5 %)	54 (37.5 %)	2 (28.6 %)	0.532	55 (77.5 %)	4 (57.1 %)			
DAPT	59 (6.9 %)	0.211	0	1 (0.6 %)	8 (2.1 %)	1 (6.7 %)	0.034	41 (17.7 %)	8 (36.4 %)	15 (3.6 %)	0.469	0	0	4 (2%)	0	0.586	10 (9.9 %)	1 (12.5 %)	25 (7.3 %)	0.606	0	0	2 (1.4 %)	0	0.021	18 (25.4 %)	5 (71.4 %)			
ANTICOAGULANTS	65 (7.6 %)	0.005	0	4 (2.3 %)	34 (8.8 %)	2 (13.3 %)	0.249	21 (9.1 %)	8 (18.2 %)	27 (6.5 %)	0.054	1 (10 %)	2 (2.2 %)	13 (6.5 %)	2 (22.2 %)	0.501	8 (7.9 %)	1 (12.5 %)	25 (7.3 %)	0.065	0	6 (7.3 %)	13 (9%)	2 (28.6 %)	1	4 (5.6 %)	0			
BETA-BLOCKERS	393 (45.8 %)	<0.001	4 (12.1 %)	49 (28.7 %)	141 (36.5 %)	10 (66.7 %)	0.850	173 (74.6 %)	16 (72.7 %)	186 (44.5 %)	<0.001	1 (10 %)	20 (22.2 %)	67 (33.5 %)	8 (88.9 %)	1	83 (82.2 %)	7 (87.5 %)	130 (38 %)	0.051	3 (9.7 %)	23 (28.1 %)	45 (31.3 %)	3 (42.9 %)	1	51 (71.8 %)	5 (71.4 %)			
CALCIUM-ANTAGONISTS	145 (16.9 %)	0.004	1 (3%)	17 (9.9 %)	74 (19.2 %)	1 (6.7 %)	0.267	50 (21.6 %)	2 (9.1 %)	59 (14.1 %)	0.219	0	9 (10 %)	33 (16.5 %)	0	0.353	17 (16.8 %)	0	66 (19.3 %)	0.037	1 (3.2 %)	10 (12.2 %)	31 (21.5 %)	1 (14.3 %)	0.414	20 (28.2 %)	3 (42.9 %)			
ANTI-ARRHYTHMICS	46 (5.4 %)	0.568	0	10 (5.9 %)	24 (6.2 %)	0	1	11 (4.7 %)	1 (4.6 %)	13 (3.1 %)	0.874	0	4 (4.4 %)	3 (3.5 %)	0	1	2 (2%)	0	17 (5%)	0.226	0	4 (4.9 %)	11 (7.6 %)	1 (14.3 %)	1	1 (1.4 %)	0			
NITRATES	16 (1.9 %)	0.558	0	0	5 (1.3 %)	0	0.606	11 (4.7 %)	0	17 (4.1 %)	1	0	2 (2.2 %)	4 (2%)	0	0.185	9 (8.9 %)	2 (25 %)	4 (1.2 %)	1	0	1 (1.2 %)	1 (2.4 %)	0	0.009	0	1 (14.3 %)			
ACE INHIBITORS	261 (30.4 %)	<0.001	0	28 (16.4 %)	106 (27.5 %)	0	0.473	108 (46.6 %)	12 (54.6 %)	202 (48.3 %)	<0.001	0	29 (32.2 %)	94 (47 %)	7 (77.8 %)	0.404	68 (67.3 %)	4 (50 %)	93 (27.2 %)	<0.001	3 (9.7 %)	11 (13.4 %)	41 (28.5 %)	6 (85.7 %)	0.346	28 (39.4 %)	4 (57.1 %)			
ARBS	166 (19.3 %)	<0.001	2 (6.1 %)	20 (11.7 %)	102 (26.4 %)	2 (13.3 %)	1	37 (16 %)	3 (13.6 %)	53 (12.7 %)	0.423	0	10 (11.1 %)	20 (10 %)	2 (2.2 %)	0.649	19 (18.8 %)	2 (25 %)	88 (25.7 %)	0.056	5 (16.1 %)	16 (19.5 %)	48 (33.3 %)	1 (14.3 %)	0.659	16 (22.5 %)	2 (28.6 %)			
DIURETICS	107 (12.5 %)	0.003	2 (6.1 %)	10 (5.9 %)	60 (15.5 %)	3 (20 %)	0.030	26 (11.2 %)	6 (27.7 %)	74 (17.7 %)	0.081	0	8 (8.9 %)	31 (15.5 %)	3 (33.3 %)	0.046	27 (26.7 %)	5 (62.5 %)	69 (20.2 %)	0.004	2 (6.5 %)	10 (12.2 %)	41 (28.5 %)	1 (14.3 %)	0.125	12 (16.9 %)	3 (42.9 %)			
RANOLAZINE	17 (2%)	1	0	1 (0.6 %)	2 (0.5 %)	0	0.618	14 (6%)	0	13 (3.1 %)	1	0	0	1 (0.5 %)	0	0.042	9 (8.9 %)	3 (37.5 %)	10 (2.9 %)	0.606	0	0	2 (1.4 %)	0	0.546	7 (9.9 %)	1 (14.3 %)			

Table 3. Final clinical diagnosis and early management in Northern, Central, and Southern Italy

[illegible]

			33)	72)		(N=15)		32)	22)			10)	90)		(N=9)		03)	8)			31)	85)		(N=7)		71)	8)
Obstructive CAD	172 (21.3%)	<0.001	0	10 (6.1%)	85 (23.1%)	4 (30.8%)	0.499	65 (30.4%)	8 (41.1%)	98 (27.1%)	<0.001	0	1 (1.3%)	51 (29.7%)	3 (33.3%)	0.464	38 (43.2%)	5 (71.4%)	33 (9.4%)	<0.000	0	3 (3.5%)	15 (10.1%)	4 (57.1%)	0.154	8 (11.3%)	3 (37.5%)
Non obstructive CAD	315 (38.9%)	0.211	4 (12.5%)	48 (29.5%)	132 (35.9%)	4 (30.8%)	0.034	119 (55.6%)	8 (42.1%)	127 (35.1%)	0.469	0	28 (35.4%)	50 (29.1%)	4 (44.4%)	0.586	43 (48.9%)	2 (28.6%)	264 (75.4%)	0.66	27 (87.1%)	56 (65.9%)	113 (76.4%)	3 (42.9%)	0.021	60 (84.5%)	5 (62.5%)
No CAD	322 (39.8%)	0.005	28 (87.5%)	105 (64.4%)	151 (41%)	5 (38.5%)	0.249	30 (14%)	3 (15.8%)	137 (37.9%)	0.054	7 (100%)	50 (63.3%)	71 (41.3%)	2 (22.2%)	0.51	7 (8%)	0	53 (15.1%)	0.065	4 (12.9%)	26 (30.6%)	20 (13.5%)	0	1	3 (4.2%)	0
Inducible ischemia	137 (18.3%)	<0.001	3 (10%)	12 (8%)	53 (16.3%)	7 (63.6%)	0.389	55 (26.1%)	7 (35%)	130 (36.6%)	0.017	0	16 (22.2%)	66 (39.8%)	2 (40%)	0.285	41 (41.4%)	5 (62.5%)	14 (4%)	0.162	0	2 (3.4%)	2 (1.4%)	1 (14.3%)	0.225	7 (9.9%)	2 (25%)
No inducible Ischemia	611 (81.7%)	0.004	27 (90%)	139 (92.1%)	272 (83.7%)	4 (36.4%)	0.267	156 (73.9%)	13 (35%)	225 (63.4%)	0.219	5 (100%)	56 (77.8%)	100 (60.2%)	3 (60%)	0.353	58 (58.6%)	3 (37.5%)	336 (96%)	0.037	31 (100%)	83 (97.7%)	146 (98.7%)	6 (85.7%)	0.414	64 (90.1%)	6 (75%)
Revascularization	111 (12.8%)	<0.001	0	7 (4.1%)	62 (15.9%)	3 (20%)	0.35	34 (14.7%)	5 (22.7%)	73 (17.3%)	<0.001	0	1 (1.1%)	40 (19.9%)	2 (22.2%)	0.032	25 (24.3%)	5 (62.5%)	26 (7.4%)	0.105	0	3 (3.5%)	13 (8.9%)	1 (14.3%)	0.225	7 (9.9%)	2 (25%)
No Revascularization	754 (87.2%)	0.558	33 (100%)	165 (95.9%)	329 (84.1%)	12 (80%)	0.606	198 (85.3%)	17 (77.3%)	348 (82.7%)	1	10 (100%)	89 (98.8%)	161 (80.1%)	7 (77.8%)	0.185	78 (75.7%)	3 (37.5%)	324 (92.6%)	1	31 (100%)	82 (96.5%)	135 (91.2%)	6 (85.7%)	0.09	64 (90.1%)	6 (75%)
Change/No treatment	289 (33.6%)	<0.001	4 (12.1%)	41 (24%)	151 (39.1%)	11 (73.3%)	0.019	70 (30.2%)	12 (54.6%)	188 (44.8%)	0.12	2 (20%)	31 (34.4%)	93 (46.3%)	3 (33.3%)	1	55 (53.9%)	4 (50%)	60 (17.5%)	0.054	4 (12.9%)	12 (14.6%)	29 (20.1%)	4 (57.1%)	1	10 (14.1%)	1 (14.3%)
No Change/no treatment	570 (66.4%)	<0.001	29 (87.9%)	130 (76%)	235 (60.9%)	4 (26.7%)	1	162 (69.8%)	10 (45.5%)	232 (55.2%)	0.423	8 (80%)	59 (65.6%)	108 (53.7%)	6 (66.7%)	0.649	47 (46.1%)	4 (50%)	282 (82.5%)	0.056	27 (87.1%)	70 (85.7%)	115 (79.9%)	3 (42.9%)	0.659	61 (85.9%)	6 (85.7%)

Table 4A. Use of imaging tests and results in the Italian vs non-Italian cohorts.

TABLE 4A	ITALIAN COHORT									NON ITALIAN COHORT									P-VALUE
	TOTAL N=1,636	P-VALUE	PATIENTS WITHOUT PREVIOUS CAD				P-VALUE	PATIENTS WITH PREVIOUS CAD		TOTAL N=2,626	P-VALUE	PATIENTS WITHOUT PREVIOUS CAD				P-VALUE	PATIENTS WITH PREVIOUS CAD		
			PTP < 5% (N=74)	5 < PTP ≤ 15 (N=347)	PTP > 15 (N=740)	LVEF < 50 (N=31)		LVEF ≥ 50 (N=406)	LVEF < 50 (N=38)			PTP < 5% (N=156)	5 < PTP ≤ 15 (N=677)	PTP > 15 (N=1,060)	LVEF < 50 (N=49)		LVEF ≥ 50 (N=587)	LVEF < 50 (N=97)	
Exercise ECG																			
Performed	647 (39.6%)	<0.001	48 (64.9%)	174 (50.1%)	270 (36.5%)	7 (22.6%)	0,093	140 (34.5%)	8 (21.1%)	669 (25.5%)	<0.001	72 (46.2%)	198 (29.3%)	255 (24.1%)	7 (14.3%)	0,002	129 (22.0%)	38 (8.3%)	<0.001
Positive	92 (5.6%)	0,287	7 (9.5%)	18 (5.2%)	44 (6.0%)	0	0,709	22 (5.4%)	1 (2.6%)	203 (7.7%)	0,148	7 (4.5%)	45 (6.7%)	94 (8.9%)	4 (8.2%)	0,216	49 (8.4%)	4 (4.1%)	0,008
Stress ECHO																			
Performed	255 (15.6%)	0,703	11 (14.9%)	46 (13.3%)	118 (16.0%)	5 (16.1%)	0,792	68 (16.8%)	7 (18.4%)	453 (17.3%)	0,097	17 (10.9%)	102 (15.1%)	159 (15%)	2 (4.1%)	0,011	138 (23.5%)	35 (36.1%)	0,156
First test	252 (15.4%)	0,658	11 (14.9%)	45 (13.0%)	117 (15.8%)	4 (12.9%)	0,792	68 (16.8%)	7 (18.4%)	438 (16.7%)	0,099	17 (10.9%)	102 (15.1%)	152 (14.3%)	2 (4.1%)	0,007	131 (22.3%)	34 (35.1%)	0,271
Positive HR	31 (1.9%)	0,007	0	1 (0.3%)	18 (2.4%)	2 (6.5%)	0,595	9 (2.2%)	1 (2.6%)	69 (2.6%)	0,011	0 (0%)	5 (0.7%)	26 (2.5%)	1 (2%)	0,005	26 (4.4%)	11 (11.3%)	0,124
Stress CMR																			
Performed	62 (3.8%)	0,853	0	7 (2.0%)	13 (1.8%)	0	0,163	36 (8.9%)	6 (15.8%)	2 (0.1%)	1	0	0	1 (0.1%)	0	1	1 (0.2%)	0	<0.001
First test	58 (3.5%)	0,868	0	6 (1.7%)	12 (1.6%)	0	0,127	34 (8.4%)	6 (15.8%)	0	-	0	0	0	0	-	0	0	<0.001
Positive HR	9 (0.6%)	1	0	0	1 (0.1%)	0	0,003	4 (1.0%)	4 (10.5%)	0	-	0	0	0	0	-	0	0	<0.001
Stress SPECT																			
Performed	297 (18.2%)	0,003	4 (5.4%)	45 (13.0%)	132 (17.8%)	8 (25.8%)	0,008	92 (22.7%)	16 (42.1%)	736 (28.0%)	0,057	32 (20.5%)	186 (27.5%)	314 (29.6%)	18 (36.7%)	0,518	157 (26.8%)	29 (29.9%)	<0.001
First test	284 (17.4%)	0,005	4 (5.4%)	43 (12.4%)	124 (16.8%)	8 (25.8%)	0,005	89 (21.9%)	16 (42.1%)	717 (27.3%)	0,057	31 (19.9%)	183 (27%)	305 (28.8%)	18 (36.7%)	0,387	151 (25.7%)	29 (29.9%)	<0.001
Positive HR	126 (7.7%)	<0.001	0	10 (2.9%)	53 (7.2%)	5 (6.1%)	0,002	47 (11.6%)	11 (29.0%)	113 (4.3%)	0,231	3 (1.9%)	17 (2.5%)	39 (3.7%)	3 (6.1%)	0,461	42 (7.2%)	9 (9.3%)	<0.001

								)	)										
Stress PET																			
Performed	0	-	0	0	0	0	-	0	0	14 (0.5%)	0,524	2 81.3%)	3 (0.4%)	8 (0.8%)	0	1	1 (0.2%)	0	0.002
First test	0	-	0	0	0	0	-	0	0	11 (0.4%)	0,306	1 (0.6%)	1 (0.2%)	8 (0.8%)	0	1	1 (0.2%)	0	0.009
Positive HR	0	-	0	0	0	0	-	0	0	2 (0.1%)	1	0	0	1 (0.1%)	0	1	1 (0.2%)	0	0.527
Stress CT perfusion																			
Performed	29 (1.8%)	0,877	0	5 (1.4%)	9 (1.2%)	0	0,629	15 (3.7%)	0	1 (0.04%)	0,454	0	1 (0.2%)	0	0	-	0	0	<0.001
First test	29 (1.8%)	0,877	0	5 (1.4%)	9 (1.2%)	0	0,629	15 (3.7%)	0	1 (0.04%)	0,454	0	1 (0.2%)	0	0	-	0	0	<0.001
Positive HR	8 (0.5%)	0,615	0	1 (0.3%)	1 (0.1%)	0	1	6 (1.5%)	0	1 (0.04%)	0,454	0	1 (0.2%)	0	0	-	0	0	0.003
CT coronary angiography																			
Performed	572 (35.0%)	0,034	19 (25.7%)	129 (37.2%)	304 (41.1%)	15 (48.4%)	0,16	100 (24.6%)	5 (13.2%)	531 (20.2%)	<0.001	42 (26.9%)	204 (30.1%)	222 (20.9%)	4 (8.2%)	0,01	57 (9.7%)	2 (2.1%)	<0.001
First test	536 (32.8%)	0,086	19 (25.7%)	119 (34.3%)	284 (38.4%)	14 (45.2%)	0,024	97 (23.9%)	3 (7.9%)	510 (19.4%)	<0.001	41 (26.3%)	199 (29.4%)	213 (20.1%)	4 (8.2%)	0,022	51 (8.7%)	2 (2.1%)	<0.001
Positive HR	91 (5.6%)	0,001	0	6 (1.7%)	49 (6.6%)	1 (3.2%)	0,06	35 (8.6%)	0	56 (2.1%)	0,002	0	5 (0.7%)	31 (2.9%)	1 (2.0%)	1	17 (2.9%)	2 (2.1%)	<0.001
Invasive coronary angiography																			
Performed	375 (22.9%)	<0.001	2 (2.7%)	38 (11.0%)	192 (26.0%)	15 (48.4%)	0,008	110 (27.1%)	18 (47.4%)	905 (34.5%)	<0.001	16 (10.3%)	147 (21.7%)	397 (37.5%)	26 (53.1%)	0,958	274 (46.7%)	45 (46.4%)	<0.001
First test	101 (6.2%)	0,005	1 (1.4%)	12 (3.5%)	49 (6.6%)	5 (1.6%)	0,518	30 (7.4%)	4 (10.5%)	652 (24.8%)	<0.001	11 (7.1%)	93 (13.7%)	290 (27.4%)	24 (49.0%)	0,231	206 (35.1%)	28 (28.9%)	<0.001
Positive HR	194 (11.9%)	<0.001	0	10 (2.9%)	96 (13.0%)	5 (16.1%)	0,208	73 (18.0%)	10 (26.3%)	411 (15.7%)	<0.001	4 (2.6%)	32 (4.7%)	184 (17.4%)	8 (16.3%)	0,316	153 (26.1%)	30 (30.9%)	0.001
FFR measured (among ICA performed)	31/375 (8.3%)	0,612	0	2/38 (5.3%)	15/192 (7.8%)	2/15 (13.3%)	1	11/110 (10.0%)	1/18 (5.6%)	57/905 (6.3%)	0,178	3/16 (18.8%)	10/147 (6.8%)	22/397 (5.5%)	1/26 (3.9%)	1	18/274 (6.6%)	3/45 (6.7%)	0.205
FFR abnormal (among FFR measured)	8/31 (25.8%)	0,742	-	0/2	4/15 (26.7%)	1/2 (50.0%)	1	3/11 (27.3%)	0/1	14/57 (24.6%)	0,557	1/3 (33.3%)	1/10 (10.0%)	7/22 (31.8%)	0	1	4/18 (22.2%)	1/3 (33.3%)	0.897
iFR measured (among ICA performed)	4/375 (1.1%)	1	0/2	0/38	1/192 (0.5%)	0/15	1	3/110 (2.7%)	0/18	15/905 (1.7%)	0,342	1/16 (6.3%)	2/147 (1.4%)	5 (1.3%)	0/26	0,599	7/274 (2.6%)	0/45	0.612
iFR abnormal (among iFR measured)	2/4 (50.0%)	-	-	-	0/1	-	-	2/3 (66.7%)	-	5 (33.3%)	1	0/1	0/2	2/5 (40%)	-	-	3/7 (42.9%)	-	0.603
Adherence (Overall diagnostic process, endpoint b)	1,016 (62.1%)	<0.001	44 (59.5%)	320 (92.2%)	462 (62.3%)	23 (74.2%)	0,359	151 (37.2%)	17 (44.7%)	1,498 (57.0%)	<0.001	59 (37.8%)	527 (77.8%)	605 (57.1%)	29 (59.2%)	0,213	233 (36.7%)	45 (46.4%)	0.001
Adherence (Choice first test, endpoint A)	1143 (69.9%)	<0.001	45 (60.8%)	332 (95.7%)	537 (72.6%)	19 (61.3%)	<0.001	206 (50.7%)	4 (10.5%)	1635 (62.3%)	<0.001	57 (36.5%)	569 (84.1%)	670 (63.2%)	28 (57.1%)	<0.001	283 (48.2%)	28 (28.9%)	<0.001

Table 4B. Use of imaging tests and results in Northern, Central, and Southern Italy

TABL E 4B	NORTHERN ITALY								CENTRAL ITALY								SOUTHERN ITALY										
	TO TAL (N= 865)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENT S WITH PREVIOUS S CAD		TO TAL (N= 421)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENT S WITH PREVIOUS S CAD		TO TAL (N= 350)	P- VALUE	PATIENTS WITHOUT PREVIOUS CAD				P- VALUE	PATIENT S WITH PREVIOUS S CAD	
			PTP < 5% (N= 33)	5 < PTP ≤ 15 (N= 391)	PTP > 15 (N= 391)	LV EF ≥ 50 (N= 172)		LVE F ≥ 50 (N= 232)	LV EF ≥ 50 (N= 22)			PTP < 5% (N= 10)	5 < PTP ≤ 15 (N= 90)	PTP > 15 (N= 201)	LV EF ≥ 50 (N= 8)		LVE F ≥ 50 (N= 103)	LV EF ≥ 50 (N= 8)			PTP < 5% (N= 31)	5 < PTP ≤ 15 (N= 85)	PTP > 15 (N= 148)	LV EF ≥ 50 (N= 8)		LVE F ≥ 50 (N= 71)	LV EF ≥ 50 (N= 8)

						15)									9)											7)			
Exceci e ECG																													
Perfor med	285 (33.0 %)	<0. 001	22 (66. 7%)	69 (40. 1%)	115 (29. 4%)	5 (33. 3%)	0,6 26	69 (29. 7%)	5 (22. 7%)	138 (32.8 %)	0,0 03	2 (20. 0%)	43 (47. 8%)	56 (27. 9%)	1 (11. 1%)	0,2 71	35 (34. 0%)	1 (12. 5%)	224 (64.0 %)	0,0 12	24 (77. 4%)	62 (72. 9%)	99 (66. 9%)	1 (14. 3%)	0,2 66	36 (50. 7%)	2 (25 %)		
Positiv e	48 (5.6 %)	0,0 37	6 (18. 2%)	8 (4.7 %)	20 (5.1 %)	0	1	13 (5.6 %)	1 (4.6 %)	20 (4.8 %)	1	0	4 (4.4 %)	11 (5.5 %)	0	1	5 (4.9 %)	0	24 (6.9 %)	0,7 85	1 (3.2 %)	6 (7.1 %)	13 (8.8 %)	0	1	4 (5.6 %)	0		
Stress ECHO																													
Perfor med	103 (11.9 %)	0,7 94	4 (12. 1%)	19 (11. 1%)	50 (12. 8%)	3 (20 %)	0,7 14	24 (10. 3%)	3 (13. 6%)	92 (21.9 %)	0,5 78	3 (30 %)	16 (17. 8%)	48 (23. 9%)	2 (22. 2%)	0,6 69	21 (20. 4%)	2 (25 %)	60 (17.1 %)	0,9 72	4 (12. 9%)	11 (12. 5%)	20 (13. 5%)	0	1	23 (32. 4%)	2 (25 %)		
First test	101 (11.7 %)	0,8 46	4 (12. 1%)	18 (10. 5%)	50 (12. 8%)	2 (13. 3%)	0,7 14	24 (10. 3%)	3 (13. 6%)	91 (21.6 %)	0,6 12	3 (30 %)	16 (17. 8%)	47 (23. 4%)	2 (22. 2%)	0,6 69	21 (20. 4%)	2 (25 %)	60 (17.1 %)	0,9 72	4 (12. 9%)	11 (12. 5%)	20 (13. 5%)	0	1	23 (32. 4%)	2 (25 %)		
Positiv e HR	14 (1.6 %)	0,0 53	0	0	10 (2.6 %)	1 (6.7 %)	1	3 (1.3 %)	0	15 (3.6 %)	0,2 32	0	1 (1.1 %)	8 (4%)	1 (11. 1%)	0,3 17	4 (3.9 %)	1 (12. 5%)	2 (0.6 %)	-	-	-	-	-	1	2 (2.8 %)	0		
Stress CMR																													
Perfor med	60 (6.9 %)	0,7 71	0	7 (4.1 %)	13 (3.3 %)	0	0,1 29	34 (14. 7%)	6 (27. 3%)	2 (0.5 %)	-	-	-	-	-	1	2 (1.9 %)	0	0	-	-	-	-	-	-	-	-		
First test	57 (6.6 %)	0,8 14	0	6 (3.5 %)	12 (3.1 %)	0	0,1 21	33 (14. 2%)	6 (27. 3%)	1 (0.2 %)	-	-	-	-	-	1	1 (1%)	0	0	-	-	-	-	-	-	-	-		
Positiv e HR	8 (0.9 %)	1	0	0	1 (0.3 %)	0	0,0 01	3 (1.3 %)	4 (18. 2%)	1 (0.2 %)	-	-	-	-	-	1	1 (1%)	0	0	-	-	-	-	-	-	-	-		
Stress SPEC T																													
Perfor med	152 (17.6 %)	0,0 61	4 (12. 15)	22 (12. 8%)	64 (16. 4%)	6 (40. 0%)	0,0 3	47 (20. 3%)	9 (40. 9%)	127 (30.2 %)	0,0 22	0	19 (21. 1%)	65 (32. 3%)	1 (11. 1%)	0,1 52	37 (35. 9%)	5 (62. 5%)	18 (5.1 %)	0,1 45	0	4 (4.7 %)	3 (2.0 %)	1 (14. 3%)	0,2 66	8 (11. 3%)	2 (25. 0%)		
First test	150 (17.3 %)	0,0 61	4 (12. 15)	22 (12. 8%)	64 (16. 4%)	6 (40. 0%)	0,0 18	45 (19. 4%)	9 (40. 9%)	116 (27.6 %)	0,0 61	0	17 (18. 9%)	57 (28. 4%)	1 (11. 1%)	0,4 3	36 (35. 0%)	5 (62. 5%)	18 (5.1 %)	0,1 45	0	4 (4.7 %)	3 (2.0 %)	1 (14. 3%)	0,2 66	8 (11. 3%)	2 (25. 0%)		
Positiv e HR	79 (9.1 %)	0,0 02	0	9 (5.2 5)	33 (8.4 %)	5 (33. 3%)	0,0 3	26 (11. 2%)	6 (27. 3%)	44 (10.5 %)	0,0 27	0	1 (1.1 %)	20 (10. 0%)	0	0,0 56	19 (18. 5%)	4 (50 %)	3 (0.9 %)	-	0	0	0	0	0,2 77	2 (2.8 %)	1 (12. 5%)		
Stress PET																													
Perfor med	0	-	0	0	0	0	-	0	0	0	-	0	0	0	0	-	0	0	0	-	0	0	0	0	-	0	0	0	
First test	0	-	0	0	0	0	-	0	0	0	-	0	0	0	0	-	0	0	0	-	0	0	0	0	-	0	0	0	
Positiv e HR	0	-	0	0	0	0	-	0	0	0	-	0	0	0	0	-	0	0	0	-	0	0	0	0	-	0	0	0	
Stress CT perfusi on																													
Perfor med	28 (3.2 %)	1	0	4 (2.3 %)	9 (2.3 %)	0	0,3 76	15 (6.5 %)	0	1 (0.2 %)	0,3 52	0	1 (1.1 %)	0	0	-	0	0	0	-	0	0	0	0	-	0	0	0	
First test	28 (3.2 %)	1	0	4 (2.3 %)	9 (2.3 %)	0	0,3 76	15 (6.5 %)	0	1 (0.2 %)	0,3 52	0	1 (1.1 %)	0	0	-	0	0	0	-	0	0	0	0	-	0	0	0	
Positiv e HR	8 (0.9 %)	0,5 91	0	1 (0.6 %)	1 (0.3 %)	0	1	6 (2.3 %)	0	0						-	0	0	0	-	0	0	0	0	-	0	0	0	
CT corona ry angio graphy																													
Perfor med	404 (46.7 %)	0,0 37	10 (30. 3%)	87 (50. 6%)	209 (53. 3%)	5 (33. 3%)	0,1 74	88 (37. 7%)	5 (22. 7%)	119 (28.3 %)	0,0 3	5 (50 %)	28 (31. 1%)	68 (33. 8%)	7 (77. 8%)	1	11 (10. 7%)	0	49 (14.0 %)	0,3 14	4 (12. 9%)	14 (16. 5%)	27 (18. 2%)	3 (42. 9%)	1	1 (1.4 %)	0		
First test	386 (44.6 %)	0,0 61	10 (30. 3%)	80 (46. 5%)	201 (51. 4%)	5 (33. 3%)	0,0 34	87 (37. 5%)	3 (13. 6%)	103 (24.5 %)	0,0 5	5 (50 %)	26 (28. 9%)	57 (28. 4%)	6 (66. 7%)	1	9 (8.7 %)	0	47 (13.4 %)	0,2 98	4 (12. 9%)	13 (15. 3%)	26 (17. 6%)	3 (42. 9%)	1	1 (1.4 %)	0		
Positiv e HR	75 (8.7 %)	0,0 05	0	5 (2.9 %)	39 (10. 0%)	1 (6.7 %)	0,0 9	30 (12. 9%)	0	14 (3.3 %)	0,5 97	0	1 (1.1 %)	8 (4.0 %)	0	1	5 (4.9 %)	0	2 (0.6 %)	0,6 56	0	0	2 (1.4 %)	0	-	0			
Invasiv e corona ry angio graphy																													
Perfor med	171 (19.8 %)	<0. 001	1 (3.0 %)	16 (9.3 %)	90 (23. 0%)	7 (46. 7%)	0,0 3	48 (20. 7%)	9 (40. 9%)	139 (33.0 %)	0,0 01	0	15 (16. 7%)	70 (34. 8%)	3 (33. 3%)	0,4 66	46 (44. 7%)	5 (62. 5%)	65 (18.6 %)	<0. 001	1 (3.2 %)	7 (8.2 %)	32 (21. 6%)	5 (71. 4%)	0,1 07	16 (22. 5%)	4 (50. 0%)		

First test	29 (3.4 %)	0,0 49	0	2 (1.2 %)	14 (3.6 %)	2 (13.3 %)	1	10 (4.3 %)	1 (4.6 %)	28 (6.7 %)	1	0	5 (5.6 %)	11 (5.5 %)	0	0,5 95	12 (11.7 %)	0	44 (12.6 %)	0,0 04	1 (3.2 %)	5 (5.9 %)	24 (16.2 %)	3 (42.9 %)	0,0 77	8 (11.3 %)	3 (37.5 %)
Positive HR	106 (12.3 %)	<0.001	0	6 (3.5 %)	57 (14.6 %)	3 (20.0 %)	0,3 59	35 (15.1 %)	5 (22.7 %)	67 (15.9 %)	<0.001	0	1 (1.1 %)	30 (14.9 %)	2 (22.2 %)	0,0 56	29 (28.2 %)	5 (62.5 %)	21 (6.0 %)	0,5 33	0	3 (3.5 %)	9 (6.1 %)	0	0,5 86	9 (12.7 %)	0
FFR measured (among ICA performed)	5 (2.9 %)	1	0	0	2 (2.2 %)	0	1	3 (6.3 %)	0	11 (7.9 %)	1	0	1 (6.7 %)	5 (7.1 %)	0	1	5 (10.9 %)	0	15 (23.1 %)	0,7 94	0	1 (14.3 %)	8 (25.0 %)	2 (40.0 %)	1	3 (18.8 %)	1 (25.0 %)
FFR abnormal (among FFR measured)	2 (40.0 %)	1	0	0	1 (50 %)	0	1	1 (33.3 %)	0	5 (45.5 %)	1	0	0	3 (60 %)	0	1	2 (40.0 %)	0	1 (6.7 %)	0,2 73	0	0	0	1 (50.0 %)	-	0	0
iFR measured (among ICA performed)	3 (1.8 %)	-	0	0	0	0	1	3 (6.3 %)	0	0	-	0	0	0	0	-	0	0	1 (1.5 %)	1	0	0	1 (3.1 %)	0	-	0	0
iFR abnormal (among iFR measured)	2 (6.7 %)	-	0	0	0	0	1	2 (66.7 %)	0	0	-	0	0	0	0	-	0	0	0	-	0	0	0	0	-	0	0

HIGHLIGHTS

1. The 2019 ESC chronic coronary syndrome (CCS) Guidelines propose a pre-test probability-based diagnostic strategy; however, in both the Italian and non-Italian cohorts, a substantial proportion of patients deviate from this recommended approach.
2. In Italy, as in other countries, the diagnostic CCS scenario is largely driven by the frequent use of exercise ECG and the direct referral of a significant proportion of patients to invasive coronary angiography without prior non-invasive stress imaging, highlighting implementation gaps and unequal access to cardiac imaging
3. Within Italy, these gaps are more pronounced in the southern regions.