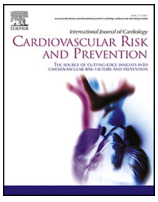
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Outpatients' cardiac rehabilitation: the long-term experience of the Niguarda Hospital

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ABSTRACT

Background: Cardiac rehabilitation (CR) is a cornerstone of secondary prevention, yet long-term real-world data on outpatient programs remain limited. We report the long-term experience of a high-volume centre, evaluating clinical profiles, temporal trends, and functional and metabolic outcomes of patients undergoing outpatient CR.
Methods: We analysed 1461 consecutive patients enrolled in the Niguarda Hospital outpatient CR program from 2012 to 2025. Demographic, clinical, angiographic, biochemical, hemodynamic, functional, and pharmacological data were collected at admission and discharge.
Results: Acute coronary syndrome was the leading indication (70.8%), though its prevalence declined over time, paralleled by a progressive rise in chronic coronary syndrome and non-ischemic indications. Patients became older and more comorbid, yet consistently achieved significant improvements in functional capacity (Δ6MWT +28.4 ± 24.4%, $p < 0.001$), left ventricular ejection fraction (from 53.3 to 55.2%, $p < 0.001$), and lipid profile (LDL cholesterol from 99.6 ± 42.0 to 64.8 ± 26.2 mg/dL, $p < 0.001$). Rates of complete revascularization increased markedly, smoking patterns shifted toward cessation, and uptake of advanced cardioprotective therapies rose substantially. Despite reduced volumes and higher baseline complexity during COVID-19 (2020–21), CR effectiveness was preserved.
Conclusions: Over 13 years, outpatient CR consistently delivered robust functional and metabolic benefits, even in an increasingly older and more complex population. Shifts in patient characteristics, improved revascularization rates, and evolution of pharmacological therapy underscore the expanding role of CR as a comprehensive, guideline-driven component of modern cardiovascular care.

1. Introduction

Cardiovascular (CV) diseases remain the leading cause of morbidity, mortality, and disability worldwide, despite major advances in acute care, and secondary prevention strategies [1]. Among evidence-based interventions, cardiac rehabilitation (CR) represents a cornerstone of comprehensive CV care. Contemporary guidelines from both European and American societies endorse CR with a Class I, Level A recommendation for patients with acute coronary syndrome (ACS), chronic coronary syndrome (CCS), heart failure (HF), peripheral arterial disease (PAD) and those undergoing coronary or valvular interventions [2–4].

CR produces a wide spectrum of clinically meaningful benefits, including improved functional capacity, enhanced quality of life, better control of CV risk factors, and a consistent reduction in hospital readmissions and CV mortality. Meta-analyses show that participation in supervised CR significantly reduces CV mortality and hospital readmissions [5]. Functional improvement, commonly assessed through measures of exercise capacity, is a robust predictor of long-term outcomes, reflecting gains in exercise capacity, endothelial function, autonomic balance, and overall cardiorespiratory fitness [6,7].

Over the past decade, the epidemiological profile of patients referred to CR has evolved substantially. Growing survival rates after ACS,

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broader indications for coronary revascularization, increased prevalence of comorbidities, and population aging have progressively reshaped the characteristics of individuals accessing CR programs [8]. Furthermore, the introduction of novel pharmacological agents—such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, sodium–glucose cotransporter-2 inhibitors (sGLT2i), and angiotensin receptor–neprilysin inhibitors (ARNI)—has contributed to an increasingly complex CV population requiring individualized multidisciplinary management.

Despite the well-recognized benefits of CR, participation rates remain suboptimal, often below 50% in Europe and even lower in outpatient settings [9]. Barriers include logistical constraints, socioeconomic factors, limited awareness among clinicians and patients, and institutional variability in program structure and referral pathways. The COVID-19 pandemic further challenged CR delivery, leading to reduced admissions, delayed referrals, and heterogeneity in patient selection, although tele-rehabilitation and hybrid models partially mitigated these effects [10–12].

Long-term real-world data on outpatient CR programs are particularly valuable, as they allow assessment of temporal trends in patient profiles, indications, functional recovery, and treatment optimization across different healthcare eras. Understanding how CR cohorts have changed over time is essential for improving program design, identifying unmet needs, and strengthening secondary prevention strategies.

The present study reports the long-term experience of the outpatient CR program at Niguarda Hospital, analysing demographic, clinical, angiographic, biochemical, hemodynamic, and functional parameters in a large cohort of 1461 consecutive patients from 2012 (opening of our CR program) to 2025. We aimed to evaluate the association between participation in outpatient CR and improvements in functional capacity and cardiometabolic profile, and to examine temporal trends in the characteristics, clinical history, risk factors, and therapeutic management of patients accessing CR over more than a decade.

2. Methods

2.1. Study population

This study had a prospective, longitudinal and observational design. 1461 consecutive patients, who attended the outpatient CR program at the Niguarda Hospital from 1st of January 2012 (opening of the program) until 31st of December 2025, were enrolled.

Inclusion criteria were being recruited for a CR program at our institution and being able to sign the written informed consent. Exclusion criteria were the presence of diseases (neurological, pneumological or orthopaedic) that do not permit to attend the CR program and individuals that prematurely discontinue the CR program.

The indication for cardiac rehabilitation was classified as ACS, CCS, HF, PAD, or other causes (hypertrophic cardiomyopathy, cardiac surgery and transcatheter aortic valve implantation).

At admission, we systematically collected demographic and clinical characteristics, including age, sex, body mass index (BMI), and CV risk factors (diabetes mellitus, arterial hypertension, dyslipidemia, and active or former smoking). CV medical history was also recorded, specifically recurrent myocardial infarction (MI), MI before the age of 45 years, previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), PAD, previous cerebrovascular events (stroke or transient ischaemic attack), atrial fibrillation (AF) and the presence of a cardiac implantable electronic device (CIED).

Coronary angiography data included the presence of significant stenosis in the left anterior descending (LAD), right coronary (RC), circumflex (CX), and left main (LM) arteries, number of vessels involved, and whether complete revascularization was achieved.

Biochemical parameters, collected both at admission and discharge, were serum creatinine, fasting glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, peak creatine kinase-MB (CK-MB), and peak high-sensitivity troponin T (hs-TnT). Hemodynamic data included systolic and diastolic blood pressure (BP) and resting heart rate (HR). Left ventricular ejection fraction (EF) was assessed, and functional capacity was measured by the 6-min walking test (6MWT), with absolute and relative improvement (Δ6MWT) recorded.

Referral rate, time from referral to CR initiation, adverse events and CR completion (considered as performing >90% of the prescribed exercise session) were also registered.

Finally, CV drug therapy at CR discharge was collected, including β-blockers, lipid lowering therapies (LLT – including statins, ezetimibe, evolocumab, alirocumab, inclisiran, or bempedoic acid), antiplatelet agents, antihypertensives (angiotensin converting enzyme inhibitors/angiotensin receptor blockers - ACEi/ARB -, calcium channel blockers, diuretics, doxazosin), sGLT2i, ARNI and glucagon-like peptide-1 receptor agonists (GLP1-ra).

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the local Ethics Committee.

2.2. Cardiac rehabilitation program

The cardiac rehabilitation (CR) program was carried out in an outpatient setting and consisted of 25 daily sessions performed over 5 days in group of 6 subjects. The core component was structured aerobic training, divided into two phases: cycle ergometer exercise and free-body exercises under physiotherapist supervision. Each phase lasted 45 min, separated by a 15-min rest period. According to guidelines [13,14], exercise load was individualized according to each patient's capacity and gradually intensified over the course of rehabilitation in order to reach the 75-85% of the peak heart rate evaluated during a 6MWT performed on the first day of CR. Cycle ergometer exercise was titrated as previously described, without significant difference determined by cardiac disease, starting from a low intensity continuous training and moving through a moderate intensity interval training till a high intensity interval training (whenever possible and tolerated by the patients).

For free-body exercises patients were divided accordingly to their exercise capacity and cardiac disease (ACS/CCS, HF and PAD) thus permitting a higher individualization [13,14]. ACS and CCS subjects mainly perform resistance exercise, in HF subjects also inspiratory muscle training was performed. Finally, in PAD subjects exercise was mainly focused on legs with regimen of walking to near-maximal pain.

Patients also attended educational sessions with a psychologist, dietitian, and cardiologist, aimed at promoting lifestyle modification, nutritional education, and therapy adherence. Diagnostic completion and therapeutical optimization were also a core component of our CR program.

Furthermore, on at the CR discharge patients received a personalized exercise prescription to let him/her to continue exercise after CR.

2.3. Six-minute walk test

Although cardiopulmonary exercise test is considered the gold-standard procedure for exercise prescription, 6MWT is a very simple and reliable test that can be used for exercise prescription in the CR context. While it has been mainly evaluated in HF patients [15] significant data have been published also in the context of ACS and CCS [16–19]. Due to logistical constraints regarding CPET performance in our center, functional capacity was assessed using the 6MWT that was also used for exercise prescription. It was performed according to international guidelines in a straight, unobstructed hospital corridor walking 30 m forth and back, for a total of 60 m every lap. The total distance covered was recorded, while HR and oxygen saturation were continuously monitored and registered at 1-min intervals during the test. 10 min' rest were mandatory before the test was performed.

2.4. Statistical analysis

Statistical analyses were performed using R© (version 4.5.1, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as absolute frequencies and percentages.

Referral rate was calculated with the following formula: (number of patients starting the CR program at our institution/(number of patients that present a CR indication – number of patients that were referred to inpatients CR at other institution) * 100.

Comparisons between admission and discharge were carried out with paired t-tests for continuous variables and χ^2 tests for categorical variables. Temporal trends across rehabilitation cohorts (2012–2025) were assessed using ANOVA for continuous variables and χ^2 tests for categorical variables. A two-sided p value < 0.05 was considered statistically significant.

3. Results

3.1. Overall study population

Table 1 shown the characteristics of the 1461 patients undergoing CR between January 2012 and December 2025. In Supplementary Table 1 both admission and discharge data (and relative p-value) were showed. The mean age was 62.1 ± 10.8 years, and 80.2% were male. CV risk factors were highly prevalent, with dyslipidaemia (73.1%), hypertension (66.8%), diabetes mellitus (20.0%), and current or former smoking (60.6%) being the most frequents. Previous cardiovascular history included PCI or CABG in 32.7%, recurrent MI in 14.1%, PAD in 8.3%, AF in 9.2%, and ischemic events before 45 years in 7.2%. A CIED was present in 5.8% of the enrolled subjects.

The main indication for CR was ACS (70.8%), followed by CCS (12.6%) while HF and PAD represented less common indications (3.1% and 1.9% respectively). Coronary angiography showed predominant involvement of the LAD (64.2%), with RC (38.7%) and CX (33.9%) also frequently affected, while LM disease was rare (6.2%). The mean number of diseased coronary vessels was 1.5 ± 0.9, and complete revascularization was achieved in 56.4% of patients.

Mean BP values were 124.1/74.2 ± 15.7/8.9 mmHg while HR was 63.6 ± 9.7 bpm. Biochemical data at admission revealed a fasting glucose of 106.1 ± 29.3 mg/dL with a creatinine of 1.01 ± 0.31 mg/dL. Mean peak hs-TnT and CK-MB were respectively 2117.3 ± 3488.4 ng/L and 107.5 ± 285.7 ng/mL. During the CR program LDL cholesterol markedly decreased (from 99.6 ± 42.0 to 64.8 ± 26.2 mg/dL, $p < 0.001$) as well as triglycerides declined (from 130.0 ± 65.6 to 114.6 ± 70.9 mg/dL, $p < 0.001$) while HDL cholesterol shown a modest, but statistically significant, rise (from 43.1 ± 12.1 to 44.5 ± 11.9 mg/dL, $p < 0.001$).

Functional capacity was limited at baseline (mean 6MWT 463.5 ± 102.8 m) with a significant improvement at discharge (6MWT distance increased to 581.3 ± 112.4 m, $p < 0.001$, with a mean relative increase of 28.4 ± 24.4%). Baseline mean EF was 53.3 ± 9.2% and significantly increased at discharge 55.2 ± 8.2% ($p < 0.001$).

Referral rate for the whole population was 39.5%, and time from index events to CR initiation was 10.4 ± 25.8 days. CR completion rate was very high (97.1%) and adverse events was rare (0.75%). In particular there were 11 adverse events of whom no deaths, 1 ACS, 3 episodes of angina (without ACS and without the needs for hospitalization), 3 episodes of atrial fibrillation (none with hospitalization needs), 1 episode of non-sustained ventricular tachycardia (interrupted with physical exercise suspension and without recurrences after β -blockers dose titration) and 3 orthopaedic complications (all of them low back pain with the needs for a 1-week CR interruption).

Medication at discharge showed high adherence to secondary prevention strategies: β-blockers (82.9%), lipid-lowering therapy (79.0%), antiplatelet drugs (92.4%), and antihypertensives (78.9%) were given to a high percentage of patients. More novel agents, such as PCSK9 inhibitors, bempedoic acid, SGLT2 inhibitors, ARNI, rivaroxaban 2.5 mg and GLP1-ra, were less frequently used and only in more recent years.

When only ACS patients (70.8% of the whole sample) were analysed (Supplementary Table 2) we found similar figures regarding prevalence of CV risk factors, previous CV diseases, BP values, biochemical examination and therapies. The significant increase in left ventricular EF and the significant increase in 6-MWT parameters were also confirmed.

Referral rate was higher in ACS patients (46.3%. vs 40.1% for CCS, 25.5% for HF and 10.1% for PAD, $p < 0.001$) while time from index events to CR initiation was lower (8.6 ± 7.8 days, $p < 0.001$) when compared with the remaining indications.

3.2. Temporal trends across biennia

When stratifying by biennia (Table 1 and Supplementary Table 1), several significant trends emerged. Patients admitted in the most recent cohorts were older (62.1 years in 2024–25 vs. 59.5 years in 2012–13, $p < 0.001$) and had a higher prevalence of dyslipidaemia (79.8% in 2024-25 vs. 60.8% in 2012-13, $p < 0.001$) and hypertension (65.8% in 2024-25 vs. 54.7% in 2012-13, $p < 0.001$).

Regarding indications (Fig. 1, panel A), ACS was predominant in all periods but progressively declined (88.1% in 2012–13 vs. 56.9% in 2024–25, $p < 0.001$), while CCS (2.8% in 2012-13 vs. 24.1% in 2024-25, $p < 0.001$) and others (3.6% in 2012-13 vs. 14.2% in 2024-25, $p < 0.001$) indications increased significantly, reflecting a broader inclusion of patients in recent years. PAD and HF remains underrepresented indications to CR in our institution.

The patients smoking profile (Fig. 1, panel B) evolved substantially over time. In the earliest cohort (2012–13), most patients with smoking history were active smokers (43.3%), while only 11.6% were former smokers. Over successive biennia, the proportion of active smokers progressively declined (to 15.2% in 2024–25, $p < 0.001$), accompanied by a marked rise in former smokers (to 54.9% in 2024–25, $p < 0.001$).

Coronary involvement shown temporal shifts, with more frequent multivessel disease in the later cohorts (mean number of diseased vessels 1.2 in 2012–13 vs. 1.7 in 2020–21, $p < 0.001$). Similarly, complete revascularization rates increased markedly, reaching 74% in 2022–23 compared to only 5% in 2012–13 (Fig. 1, panel C).

There was a significant trend for a lower improvement in 6MWT, both absolute and relative (183.3 ± 79.9 m and 44.9 ± 28.4% in 2012-13 vs. 95.7 ± 85.1 m vs. 24.0 ± 32.2% in 2024-25, $p < 0.001$) that was probably related to the higher baseline 6MWT (437.4 ± 88.2 m in 2012-13 vs. 481.9 ± 96.2 m in 2024-25, $p < 0.001$, Fig. 1, panel D).

Referral rate progressively increased across biennia (from 33.6% in 2012-2013 to 50.7% for 2024-2025, $p = 0.014$, lower values – 19.2% - reached during the COVID-19 pandemic) while time from index events to CR initiation, adverse events and CR completion rate remained stable over time with only a slight decrease in the latter in the COVID-19 years (89.8%).

In terms of pharmacotherapy, later cohorts shown a progressive increase in the prescription of recent therapies (HF therapies – Fig. 2, panel A; lipid-lowering therapies – Fig. 2, panel B; rivaroxaban 2.5 mg – Fig. 2, panel C; GLP1-ra – Fig. 2, panel D), in line with evolving clinical guidelines.

The COVID-19 biennium (2020–21) represented a critical inflection point. Patient numbers were reduced (n = 128 vs. ~200–250 in other biennia). The clinical profile during this period shown higher comorbidity burden (greater prevalence of hypertension, dyslipidaemia, and diabetes) and more PAD. Functional outcomes remained favourable but gains in 6MWT and lipid control appeared less pronounced.

When only ACS patients were analysed (Supplementary Table 2) we absolutely confirm the same temporal trend. Also in this subgroup referral rate significantly increase among biennia (with a negative result during the COVID-19 years).

Table 1
Population characteristics of the whole population and when divided by biennia.

	Whole popoulation (n = 1461)	2012/13 (n = 181)	2014/15 (n = 202)	2016/17 (n = 233)	2018/19 (n = 252)	2020/21 (n = 128)	2022/23 (n = 260)	2024/25 (n = 202)	p-value (ANOVA)
CLINICAL AND ANAMNESTIC DATA									
Age [years]	62.1 ± 10.8	59.5 ± 11.2	62.7 ± 10.8	62.0 ± 10.4	62.4 ± 10.4	60.3 ± 10.7	64.0 ± 10.2	62.1 ± 11.4	<0.001
Male gender [%]	80.2	79.9	82.8	78.3	82.6	65.7	76.1	82.2	0.585
BMI [kg/m^2]	26.9 ± 4.2	26.6 ± 4.2	27.1 ± 4.3	27.1 ± 3.8	27.1 ± 4.0	26.6 ± 5.1	27.1 ± 4.4	26.5 ± 4.1	0.437
History of CV disease [%]	45.2	46.8	44.5	43.2	48.7	43.7	40.8	48.0	0.571
Diabetes [%]	20.0	15.3	21.1	20.8	26.5	18.8	20.2	18.3	0.236
Dyslipidaemia [%]	73.1	60.8	65.2	72.8	70.2	78.3	87.1	80.2	<0.001
Hypertension [%]	66.8	54.7	71.2	72.8	65.6	58.9	74.3	66.8	<0.001
Active or former smoker [%]	60.6	54.6	49.2	63.1	63.4	71.6	60.4	69.8	<0.001
Recurrent MI [%]	14.1	11.2	16.8	19.3	7.7	16.4	13.9	10.9	0.052
PAD [%]	8.3	3.4	5.8	7.9	11.2	11.1	8.0	5.9	0.081
Previous stroke [%]	10.2	5.3	9.9	10.2	10.1	11.4	12.8	10.4	0.217
MI < 45 years [%]	7.2	4.3	6.9	6.3	5.3	9.2	7.1	10.9	0.081
Previous PCI or CABG [%]	32.7	19.2	34.1	26.8	21.9	35.2	55.1	35.7	<0.001
CIED [%]	5.8	3.2	4.1	6.9	3.8	2.9	5.0	7.8	0.056
AF [%]	9.2	2.9	7.1	7.9	8.1	8.9	10.9	13.2	0.039
CARDIAC REHABILITATION INDICATION									
ACS [%]	70.8	88.1	77.8	71.9	68.4	63.6	69.4	56.9	<0.001
CCS [%]	12.6	2.8	10.9	11.8	14.1	25.7	9.3	24.1	<0.001
Heart Failure [%]	3.1	4.2	1.8	5.2	3.7	1.2	2.9	4.1	0.416
PAD [%]	1.9	0.3	1.2	3.6	5.1	1.8	1.7	0.8	0.007
Others [%]	10.3	3.6	7.4	7.2	8.6	6.5	16,8	14.2	<0.001
CARDIAC REHABILITATION DATA									
Time from index events to CR (days)	10.4 ± 25.8	10.1 ± 21.9	10.9 ± 26.8	10.4 ± 21.5	10.2 ± 28.7	12.4 ± 30.3	10.1 ± 27.6	9.8 ± 25.5	0.098
Referral rate (%)	39.5	33.6	34.7	37.1	42.6	19.2	49.5	50.7	0.014
CR completion (%)	97.1	95.5	98.4	98.9	97.4	89.8	98.6	98.7	0.156
Adverse events	0.75	1.1	0.49	0.43	0.79	1.5	1,15	0.49	0.091
CORONARY ANGIOGRAPHY									
LAD [%]	64.2	33.2	64.3	65.8	70.2	67.9	71.4	54.0	<0.001
RC [%]	38.7	30.8	37.2	40.9	41.3	46.2	41.8	37.9	0.174
CX [%]	33.9	29.4	27.2	34.9	36.8	33.3	41.8	33.4	0.036
LM [%]	6.2	3.8	3.2	1.8	7.9	10.2	9.4	4.6	0.007
Number of coronary arteries with atherosclerotic involvement [n]	1.5 ± 0.9	1.2 ± 0.8	1.3 ± 0.8	1.4 ± 0.8	1.7 ± 0.9	1.8 ± 1.0	1.7 ± 1.0	1.4 ± 1.0	<0.001
Complete revascularization [%]	56.4	5.3	29.2	70.8	64.7	69.2	73.8	60.4	<0.001
BIOCHEMICAL VARIABLES									
Creatinine [mg/dL]	1.01 ± 0.31	0.93 ± 0.25	1.00 ± 0.27	0.97 ± 0.36	1.03 ± 0.36	1.01 ± 0.21	1.07 ± 0.35	1.04 ± 0.29	<0.001
Total cholesterol [mg/dL]	167.6 ± 46.4	193.3 ± 37.5	185.6 ± 45.5	174.5 ± 40.1	169.2 ± 41.6	160.9 ± 40.0	152.5 ± 47.8	160.3 ± 53.9	<0.001
LDL cholesterol [mg/dL]	99.6 ± 42.0	120.2 ± 36.1	116.4 ± 41.4	105.1 ± 37.0	99.5 ± 38.6	96.0 ± 35.7	88.1 ± 42.9	92.6 ± 48.6	<0.001
HDL cholesterol [mg/dL]	43.1 ± 12.1	40.7 ± 10.8	42.6 ± 11.4	44.9 ± 11.7	43.2 ± 12.4	42.3 ± 11.5	43.5 ± 13.2	41.9 ± 11.7	0.233
Triglycerids [mg/dL]	130.0 ± 65.6	139.4 ± 69.3	134.4 ± 69.9	129.6 ± 62.2	128.4 ± 61.4	131.9 ± 63.8	126.0 ± 67.1	130.3 ± 69.8	0.89
Glucose [mg/dL]	106.1 ± 29.3	100.3 ± 18.6	96.9 ± 17.6	106.6 ± 32.7	109.9 ± 29.4	103.9 ± 20.4	105.8 ± 34.5	107.4 ± 24.1	0.265
CK-MB peak [ng/mL]	107.5 ± 285.7	90.9 ± 136.9	78.6 ± 115.0	88.1 ± 135.0	105.6 ± 126.9	106.0 ± 141.6	165.0 ± 578.6	142.8 ± 427.7	0.149
TnT-hs peak [ng/L]	2117.3 ± 3488.4	1376.5 ± 331.6	1372.4 ± 2191.9	2117.4 ± 3551.7	3112.8 ± 5096.9	2320.3 ± 3861.2	1881.2 ± 3455.3	2272.5 ± 4557.0	0.209

(*continued on next page*)

Table 1 (*continued*)

	Whole popoulation (n = 1461)	2012/13 (n = 181)	2014/15 (n = 202)	2016/17(n = 233)	2018/19(n = 252)	2020/21(n = 128)	2022/23(n = 260)	2024/25(n = 202)	p-value (ANOVA)
HEMODYNAMIC DATA									
SBP [mmHg]	124.1 ± 15.7	122.5 ± 12.3	123.8 ± 11.8	123.1 ± 15.1	123.8 ± 16.6	121.5 ± 16.1	126.9 ± 15.6	124.2 ± 15.1	0.062
DBP [mmHg]	74.2 ± 8.9	71.2 ± 8.6	69.9 ± 7.9	73.8 ± 7.9	73.8 ± 8.6	74.3 ± 8.6	75.6 ± 9.1	75.1 ± 9.7	0.002
HR [bpm]	63.6 ± 9.7	59.7 ± 5.9	62.8 ± 7.9	63.6 ± 8.4	64.2 ± 9.1	64.6 ± 10.1	63.8 ± 10.1	62.9 ± 11.4	0.374
LVEF [%]	53.3 ± 9.2	53.0 ± 8.9	53.2 ± 9.4	53.0 ± 9.5	53.9 ± 8.6	54.5 ± 7.3	54.1 ± 8.6	51.2 ± 11.6	0.037
6-MINUTE WALKING TEST									
6MWT [mt]	463.5 ± 102.8	437.4 ± 88.2	401.4 ± 98.0	449.3 ± 95.4	497.3 ± 106.2	512.5 ± 89.9	469.2 ± 99.9	481.6 ± 96.4	<0.001
6MWT distance vs. predicted [%]	87.7 ± 19.9	79.2 ± 7.2	76.5 ± 17.3	85.7 ± 16.4	94.2 ± 18.6	96.6 ± 14.8	89.5 ± 20.8	87.9 ± 22.7	<0.001
Δ6MWT [mt]	118.0 ± 79.9	183.3 ± 100.6	152.0 ± 67.8	122.6 ± 61.7	95.6 ± 61.6	76.8 ± 41.9	92.7 ± 72.1	94.8 ± 86.1	<0.001
Δ6MWT (%)	28.4 ± 24.4	44.9 ± 28.4	39.9 ± 21.1	27.9 ± 13.7	21.3 ± 20.1	16.4 ± 10.5	22.4 ± 22.9	24.5 ± 32.3	<0.001
CARDIOVASCULAR DRUGS									
Beta-blockers [%]	82.9	77.7	55.4	90.9	92.5	86.7	87.2	81.9	<0.001
LLT [%]	79.0	45.6	58.9	94.4	94.0	92.2	95.8	90.6	<0.001
Anti-platelets drugs [%]	92.4	86.2	95.9	94.4	93.2	91.4	91.8	87.1	0.024
Rivaroxaban 2,5 mg [%]	1.2	–	–	–	–	1.6	2.4	1.5	0.098
Anti-hypertensive drugs [%]	78.9	69.4	80.8	84.1	84.1	78.1	72.9	72.8	0.004
ACE-inhibitors or ARB [%]	70.3	58.3	72.7	78.1	76.2	74.2	64.3	58.9	<0.001
Calcium-channel blockers [%]	16.5	11.1	3.8	1.7	17.5	21.1	28.3	24.2	<0.001
Diuretic [%]	21.6	0	3.0	15.5	26.6	10.9	32.2	31.5	<0.001
Doxazosin [%]	2.5	0	0	2.2	4.4	2.3	3.9	0.6	0.044
SGLT2i [%]	12.2	–	–	1.6	3.2	1.6	17.1	31.6	<0.001
ARNI [%]	6.6	–	–	0.8	2.8	3.9	7.0	16.7	<0.001
GLP1-ra [%]	2.6	–	–	–	–	1.6	5.4	4.3	0.023
PCSK9-i [%]	6.2	–	–	3.4	2.4	7.0	10.8	14.7	<0.001
Evolocumab [%]	2.4	–	–	1.7	1.2	2.3	4.6	6.4	<0.001
Alirocumab [%]	2.3	–	–	1.7	1.2	4.7	2.7	6.1	<0.001
Inclisiran [%]	1.5	–	–	–	–	–	3.5	3.4	0.068
Bempedoic acid [%]	1.7	–	–	–	–	–	4.2	6.7	<0.001

Abbreviations: BMI = body mass index; CV = cardiovascular MI = myocardial infarctions; PAD = peripheral artery disease; ACS = acute coronary syndrome; CCS = chronic coronary syndrome; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CIED = cardiac implantable electronic device; AF = atrial fibrillation; CK-MB = creatine kinase-MB; TnT-hs = high-sensitivity troponin T; LDL = low density lipoprotein; HDL = high density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; LVEF = left ventricular ejection fraction; 6MWT = six-minute walk test; LAD = left anterior descending; RC = right coronary; CX = circumflex; LM = left main; LLT = lipid-lowering therapy; ACE-i/ARB = angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; SGLT2i = sodium-glucose co-transporter-2 inhibitors; ARNI = angiotensin receptor–neprilysin inhibitor; GLP1-ra = glucagon-like peptide-1 receptor agonists; PCSK9-i = Proprotein Convertase Subtilisin/Kexin type 9-inhibitors.

4. Discussion

Our thirteen-year analysis of 1461 patients confirms the pivotal role of outpatient CR as an essential component of secondary prevention and post–CV event management with several results that need to be discussed. Three main findings emerge from our study: (i) participation in CR is consistently associated with significant improvements in functional capacity, left ventricular EF, and cardiometabolic profile; (ii) temporal analyses revealed an aging patient population, evolving smoking patterns (fewer active smokers but more with smoking history), wider inclusion of CCS patients, improved rates of complete revascularization and pharmacological optimization, in line with recent guideline recommendations; and (iii) the COVID-19 pandemic represented an inflection point but did not interrupt the beneficial effects of CR.

Regarding the first point, in line with international evidence [5], participation in our CR program resulted in significant gains in functional capacity, as demonstrated by a marked increase in 6MWT distance and an improvement in left ventricular EF. These benefits were consistently observed across all biennia and remained clinically meaningful even in more recent years, despite progressively higher baseline 6MWT values that naturally reduce the potential for absolute gain.

Similarly, cardiometabolic parameters improved with a significant decrease in LDL cholesterol accompanied by triglycerides improvements. These findings align with prior literature showing that CR enhances therapy adherence, facilitates risk-factor control, and contributes to reducing residual cardiovascular risk.

In the INTERASPIRE study [20] it is thoroughly demonstrated that low adherence to a cardiac rehabilitation program (~9% across more than 4000 patients in secondary prevention for coronary artery disease) leads to poor CV risk factor management and under-achievement of the guideline medical direct therapy goals (1% of the patients).

Conversely, in population where CR programs find a solid ground, the life-style changes – and their relatives benefits – tend to last and to be persistent [21].

As biomarkers are consistently taken in account alongside functional parameters to describe the health status of a population, CR programs proved to be as effective in ameliorating the overall metabolic profile: total cholesterol and LDL reduction [22], lower blood pressure and inflammatory status [23].

Temporal analysis highlights profound changes in the characteristics of patients entering the program. Although ACS remained the leading indication, its proportion progressively declined. This trend likely reflects improvements in acute and peri-procedural management, and a progressive expansion of CR access to more stable patients.

In fact, patients with CCS increased almost tenfold (from 2.8% to 24.1%), in accordance with guideline shifts emphasizing the "secondary prevention continuum," extending beyond post-ACS patients to include all individuals with documented atherosclerotic disease [24].

The SWEDEHEART registry [25] confirms the growing trend in historically less frequent indications, such as heart failure and peripheral vasculopathy.

Furthermore, mean patient age increased by nearly 3 years across the study period. This trend mirrors broader epidemiological patterns, increased survival after CV events, and improved accessibility of CR for older individuals.

Same results and trends emerged from the previous works regarding frailty [26]. In fact, frailty, which is not a merely proxy of the aging processes, is increasing in the CR programs population. Even if this may represent an expected outcome of better care and prevention programs it determines challenges reflecting more complex case, both clinically and socially, that needs a specific approach. An example of this scenario is the clear shift from ST-segment elevated myocardial infarction (STEMI) to non ST-segment elevated myocardial infarction (NSTEMI) [27] with more complicate multi-vessel disease, lower rate of complete revascularization and longer recovery time.

Together with the aging process we observed an increased prevalence of hypertension and dyslipidaemia (from 54.7% to 65.8%, and from 60.8% to 87.1%, respectively).

However, interpretation must account for evolving guideline thresholds (stricter LDL targets and lower BP cut-offs). Indeed, absolute lipid and BP values on admission were lower in the most recent cohorts, suggesting improved pre-CR control rather than a true increase in comorbidity burden [28,29].

The smoking profile changed dramatically: active smoking sharply decreased (from 43.3% to 15.2%) while former smoking increased markedly (from 11.6% to 54.9%). This reflects improved smoking-cessation strategies, earlier and more aggressive preventive measures and an aging population with a greater cumulative exposure to tobacco but also a clear trend toward smoking cessation in the more recent years [30].

Data from China [31], Europe [32] and United States [33] point in the same direction: a clear willingness of the population to quit smoking (~50% of last-year attempts) whereas only a little part (~7%) will be able to persistently quit.

Even if the data are appealing, two main limitations must be disclosed: firstly, the data regarding smoking habit are cross-sectional and therefore no longitudinal conclusions are allowed. In fact, awareness of smoking harms is raising and patients are more prone to quit in concomitance to an ACS. However, the persistence of this change over time and far from the index hospitalization, even if promising, could not be assumed. Lastly, we account only for tobacco consumption; the new generation of e-cigarettes, increasingly adopted in quit-smoking programs, has not been recorded.

The evolution of pharmacological therapies at discharge paralleled advances in cardiological disease guidelines recommendations. In particular there were a substantial increase in PCSK9 inhibitor use (up to 14.6%, with immediately use of inclisiran) and.

SGLT2 inhibitors with also significant increase in ARNI, GLP-1 receptor agonists and bempedoic acid. These trends reinforce the concept of CR as not only a supervised exercise program but also a multidisciplinary environment for comprehensive therapeutic optimization, fully aligned with updated evidence-based recommendations.

Regarding referral rate, our data confirm that only a low percentage of patients with an indication to CR really perform it. Although it increases over time, it still remain too low, as already found by previous studies [34–36]. This data was higher in ACS patients that also presents a lower time from referral to CR initiation that identified this subgroup of subjects as a prerogative of our CR program.

CR referral rate still constitute the main issue for CR participation. Previous studies have evaluated different strategies such as multidisciplinary quality improvement team [37], automatic referral [38], acute cardiologist informative course [39] and mixed models [38,39]. All these strategies determine a significant improvement and could be locally and nationally used to implement CR referral rate.

On the opposite CR completion rate was very high and stable over time and among different indication, and adverse events was very low. These data confirm the feasibility and safety of CR program performed in an outpatient setting.

Another relevant finding of our study concerns the impact of the COVID-19 pandemic on access and outcomes of CR. The 2020–21 biennium represents a clear discontinuity within our temporal analysis, characterized by a marked reduction in patient volume ($n = 128$ compared with approximately 200–250 patients in other biennia) and referral rate (19.2% vs 39.5%). This observation is consistent with reports from multiple CR centers worldwide, which documented a dramatic decline in referrals and program attendance during the pandemic, largely driven by healthcare system reorganization, prioritization of acute care, and restrictions on outpatient services [40,41]. In fact, many CR centers were closed during this period and not all of them fully recover after the pandemic [42].

Our study found that, beyond reduced access, patients admitted during the pandemic period exhibited a higher comorbidity burden,

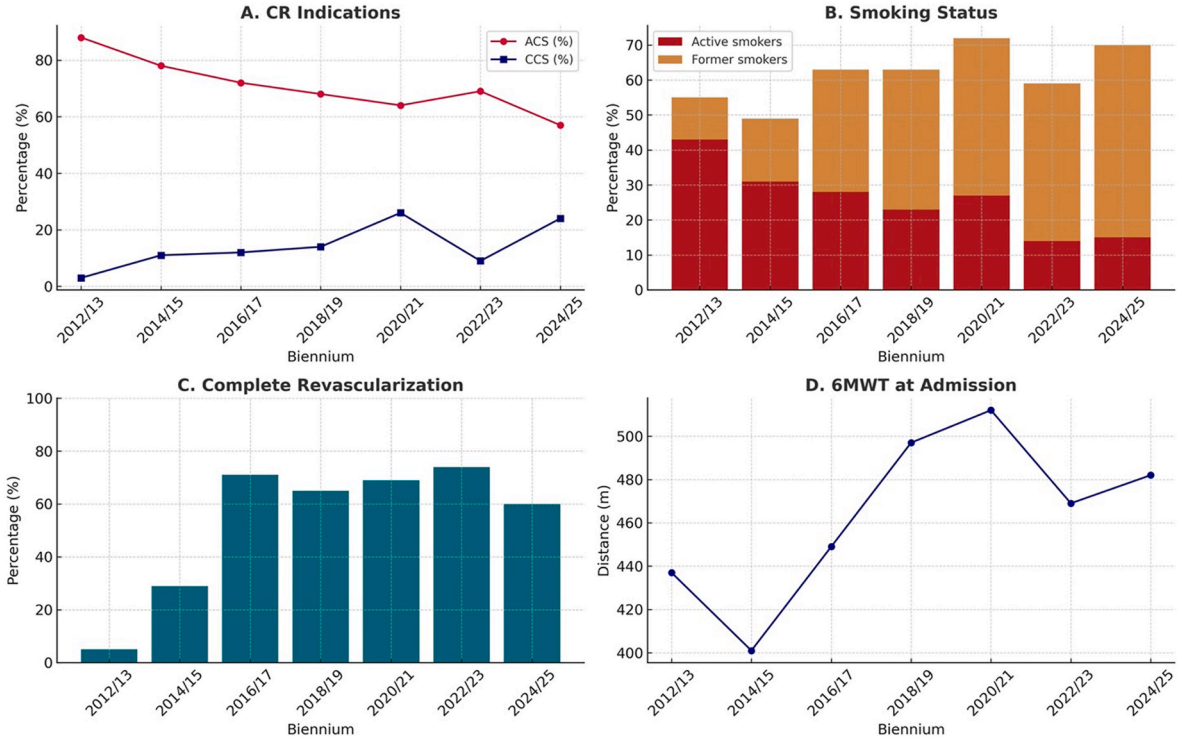


Fig. 1. Temporal trends in cardiac rehabilitation when divided accordingly to biennia (2012–2025). Indications for cardiac rehabilitation (panel A); Smoking status (panel B); Rates of complete revascularization (panel C); Admission 6-min walk test (panel D).

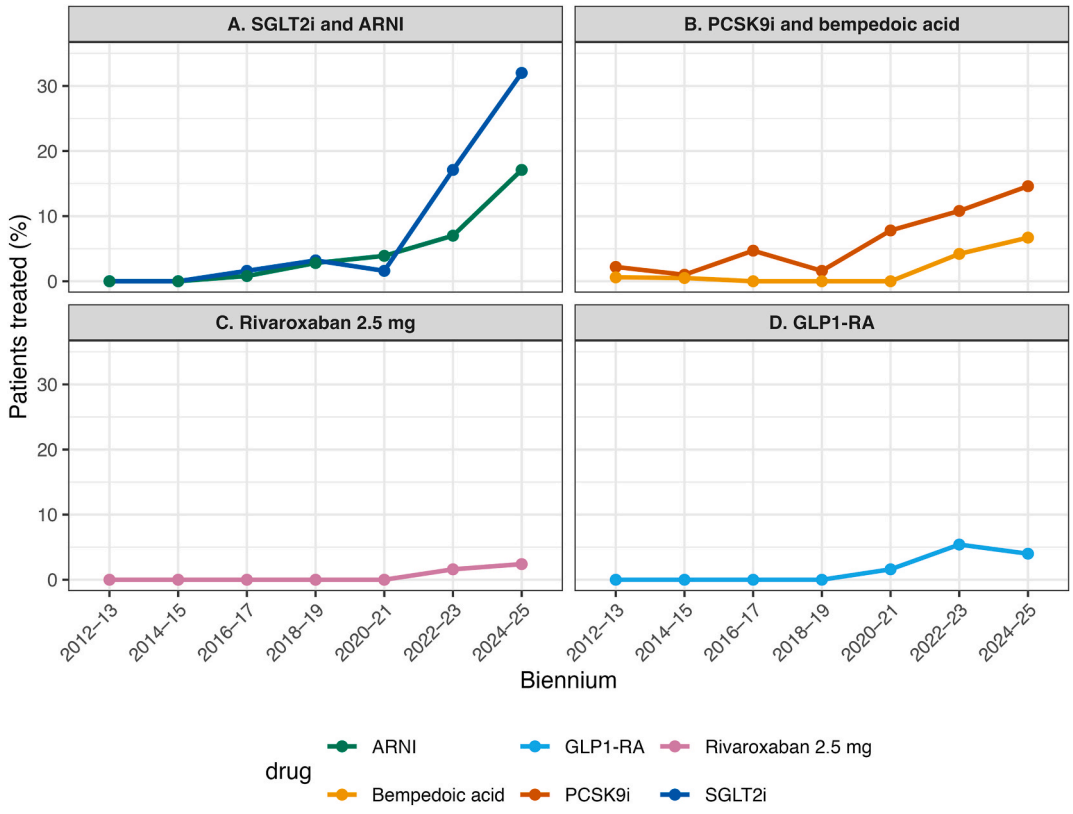


Fig. 2. Temporal trends in cardiac rehabilitation cohorts when divided accordingly to biennia (2012–2025). Heart failure drugs Indications (panel A); Lipid lowering therapies (panel B); Rivaroxaban 2.5 mg (panel C); GLP1- receptor agonist (panel D).

with greater prevalence of hypertension, dyslipidaemia, diabetes mellitus, and PAD. Similar shifts toward a more complex clinical profile have been described in other cohorts, likely reflecting delayed presentations, postponed elective procedures, and a selection bias favouring patients with higher perceived clinical risk once CR services partially resumed [43,44]. These factors may have contributed to the observed attenuation of functional and metabolic improvements, despite overall favourable outcomes.

Furthermore, improvements in functional capacity (6MWT) and lipid control remained significant but were less pronounced compared with pre-pandemic periods. This finding aligns with previous studies reporting reduced baseline physical fitness and increased deconditioning among CV patients following prolonged lockdowns, attributable to decreased physical activity levels, social isolation, and limited access to structured exercise programs [45,46]. In addition, delayed hospital admissions and postponed referrals to CR may have resulted in patients entering rehabilitation at a more advanced stage of physical decline, thereby limiting the relative magnitude of improvement achievable within a standard CR program duration.

Importantly, despite these challenges, the CR program at our institution continued with only few complete interruptions and preserved its beneficial effects on functional capacity and CV risk factor control. This resilience mirrors observations from centers that rapidly adapted CR delivery models during the pandemic, including the implementation of hybrid or tele-rehabilitation strategies and reinforced outpatient pathways. In fact, national and international organization provided specific recommendation for performing CR exercise training during the COVID-19 pandemic [42,47]. Furthermore, also recommendation regarding the necessity of implementing tele-rehabilitation CR program were provided together with tele-surveillance services. COVID-19 pandemic could be seen as a potential call-to-action and accelerator for implementing cardiac tele-rehabilitation program and, in fact, such programs were implemented during that period [11,48–51].

Collectively, these data reinforce the concept that CR is an essential component of secondary CV prevention even during periods of system-wide stress, and that maintaining access to CR services is crucial to mitigate the indirect CV consequences of public health crises.

The results of our study are influenced by some limitations, the first of which is the absence of a subsequent follow-up that will not allow us to assess long-term beneficial effects of CR. Another limitation is that we collected data on CV therapies only at the end of CR and we recorded drug classes but not specific doses. Similarly, we did not collect data on medication adherence, limiting our ability to assess whether poor compliance. Finally, ours is a monocentric study and so generalizability could be influenced by local patients' selection and procedures.

5. Conclusions

Cardiac rehabilitation in an outpatient setting consistently delivers marked and clinically relevant improvements in functional capacity, ventricular performance, and cardiometabolic status. Despite the progressive shift toward an older and more complex population, the effectiveness of the program remains unequivocally preserved. The evolving clinical profile of referred patients—together with rising rates of complete revascularization and sustained smoking cessation—underscores the expanding strategic role of CR in modern cardiovascular care. These findings firmly establish structured rehabilitation as an indispensable component of secondary prevention, with durable impact on patient trajectories.

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CRediT authorship contribution statement

Matteo Fortuna: Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Chiara Tognola:** Data curation, Formal analysis, Writing – review & editing. **Alfredo Luongo:** Data curation, Methodology, Writing – review & editing. **Marco Biolcati:** Data curation, Methodology, Writing – review & editing. **Marta Alloni:** Data curation, Methodology, Writing – review & editing. **Giovanni Pio Prencipe:** Data curation, Investigation, Writing – review & editing. **Beatrice Invernici:** Data curation, Investigation, Methodology, Writing – review & editing. **Sara D'Alesio:** Data curation, Investigation, Methodology, Writing – review & editing. **Francesco Venturelli:** Data curation, Investigation, Methodology, Writing – review & editing. **Federico Steccanella:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Vittorio Tateo:** Data curation, Writing – review & editing. **Maria Chiara Pedretti:** Data curation, Validation, Writing – review & editing. **Letizia Zadra:** Data curation, Visualization, Writing – review & editing. **Salvatore Riccobono:** Conceptualization, Methodology, Writing – review & editing. **Cristina Giannattasio:** Funding acquisition, Supervision, Writing – review & editing. **Alessandro Maloberti:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft.

Declaration of competing interest

None.

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none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2026.200692.

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