



Cardiac Rehabilitation and Percutaneous Coronary Intervention: Together Against Global Burden of Cardiovascular Disease

Elio Venturini, Roberto Testa

Elio Venturini, Roberto Testa, Department of Cardiology, Civic Hospital Cecina, via Montanara 39, 57023 Cecina (Li), Italy
Correspondence to: Elio Venturini, via Brodolini 27/c, 57023 Cecina (Li), Italy

Email: vent.elio@tin.it

Telephone: +390586614334

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INTRODUCTION

Since the original report by Andreas Gruentzig^[1] percutaneous coronary intervention (PCI) is an increasingly common treatment for coronary heart disease in the last twenty years. By now the number of procedures of PCI has overcome that of coronary artery bypass graft (CABG)^[2]: about 1.2 million PCI are performed every year in the US alone with an average fivefold increase in the number of PCI every decade. There has contemporarily been a technological improvement of the devices, from bare metal (BMS) to drug eluting (DES) and now bioresorbable stents and technical solutions during the procedure as distal protection, thrombus aspiration and intravascular ultrasound. Moreover the progress of the pharmacological therapy (clopidogrel and other platelet aggregation inhibitors IIb/IIIa inhibitors) has expanded the number of the subjects suitable to PCI. More recently, the PCI volumes of interventions have been steadily declining since 2004 in the United States^[3], but not in Europe. In the UK the number of PCI performed in 2011 (88,692 procedures in 2011) was 1,405 per million population, more than doubled in the last 10 years^[4] (Figure 1).

Therefore the increase in the use of PCI have outpaced efforts to ensure that this procedure is being used in the most appropriate manner: high risk (left main stem, triple-vessel disease, severe and complex coronary-artery disease) patients are not treated with CABG today even if the surgery has shown benefits in terms of survival^[5]. Besides in chronic stable coronary heart disease, PCI was associated with a significant reduction in angina but none a significant decrease in the risk of myocardial infarction, death, and bypass surgery^[6]. Often, out in the setting of the acute coronary syndrome, the majority of patients treated with PCI were asymptomatic or had minimal symptoms and, experienced little improvement in health status after the procedure^[7]. The COURAGE^[8] study confirmed that in patients with stable coronary artery disease, a management strategy with PCI towards optimal drug therapy associated with lifestyle intervention is not superior in reducing the risk of cardiovascular events (death, myocardial infarction, and stroke). A recent meta-analysis^[9] of 5286 P with stable coronary heart disease in which, in 4064, the ischemia was documented by stress test or fractional flow reserve, the PCI was not associated with a reduction in death, nonfatal MI, unplanned revascularization, or angina compared to medical therapy alone. This

ABSTRACT

Percutaneous coronary interventions (PCI) have become the most frequently used technique of revascularization. Nevertheless, has not shown to be superior to optimized medical therapy in the case of stable atherosclerotic coronary artery disease. Moreover, even after acute myocardial infarction (AMI), coronary risk profile often remains elevated exposing the patients (P) to events such as death and reinfarction. The cardiac rehabilitation (CR) has been shown to reduce all-cause mortality, cardiovascular mortality and events after AMI. But it is able to improve the outcome in patients undergoing PCI. The objective of this manuscript is to summarize the current knowledge with respect to CR after PCI, in terms of improvement of risk factors, functional capacity and prognosis. The biochemical mechanisms that underlying the exercise-induced benefits will be briefly described. We will critically assess the reasons why the low use of CR and the poor secondary prevention after angioplasty. We will demonstrate how PCI and CR together are the most effective intervention to fight the recurrence of cardiovascular disease (CVD).

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Key words: Cardiac Rehabilitation; Coronary artery disease; Myocardial Infarction; Exercise; Percutaneous Coronary Intervention; Secondary Prevention

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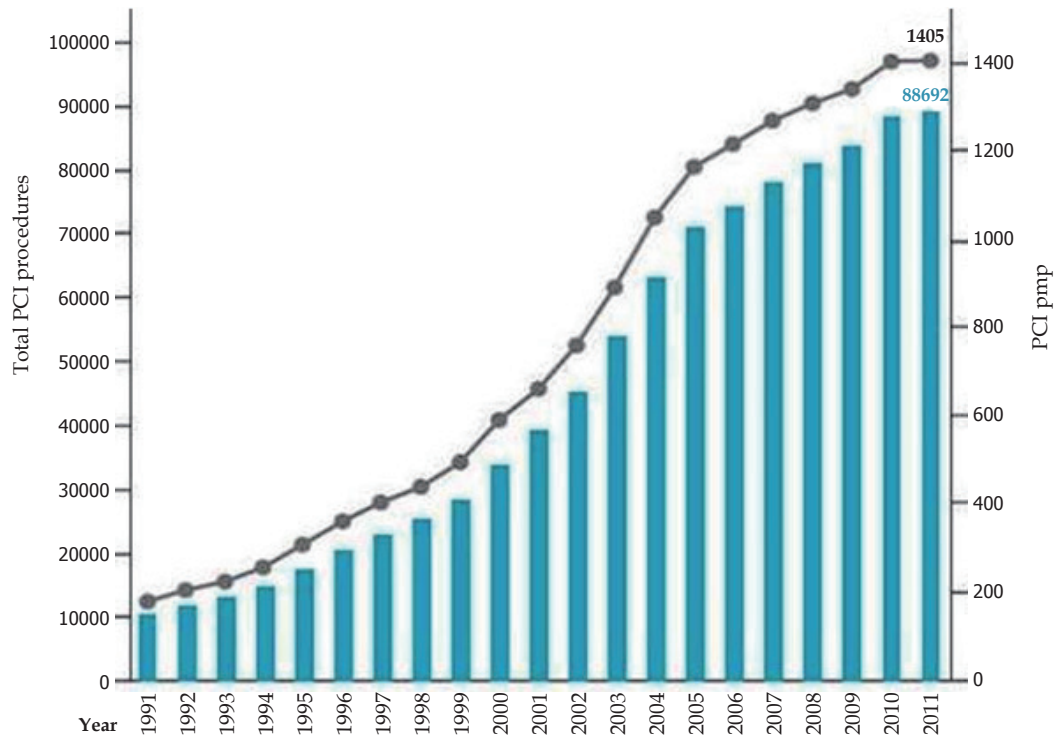


Figure 1 Increase in PCI activity 1991-2011 in the UK. Source: United Kingdom's National Audit of Percutaneous Coronary Intervention, 2011.

emphasizes the need to reduce significantly the risk profile after PCI. Anyway, although the risk of P after a cardiac attack is very high they often are not receiving appropriate evidence-based therapeutic interventions or health behaviour advices and, as a consequence, most are not achieving the recommended secondary prevention goals. The integration of cardiovascular disease prevention strategies into daily practice is still inadequate.

In the EUROASPIRE III survey^[10] despite an increase of use of lipid-lowering drugs after hospital discharge 51% of patients had elevated serum total cholesterol (≥ 4.5 mmol/L) despite an use of 78% of statins and even higher of other cardioprotective drugs. Furthermore the prevalence of smoking, hypertension and obesity are unacceptably high: 17%, 31% and 53% respectively. The survey shows that although there are numerous evidence-based guidelines their use in the context of secondary prevention of cardiovascular disease is poor. In addition the Interheart^[11] study show us that in all regions of the world, also in low and medium income countries, the traditional coronary risk factors accounted of more than 90% of population attributable risks for AMI: the approach to prevention must be similar worldwide.

The majority of heart attack survivors do not receive appropriate care and counselling: less than 30% of patients after AMI in the US^[12] undergoes cardiac care and counselling. Women and older patients have the lowest participation rate in Cardiac Rehabilitation (CR) despite the good results in terms of cost and outcome also of programs Home-based^[13]. The changes in lifestyle and risk factors after PCI in subjects none enrolled in (CR) programs are negligible^[14]. After one year, 54.4% of the patients did not perform regular exercise, 75 % had a high BMI, 47.2% not reached the target of C-LDL and 37.6% remained smokers. In conclusion a large proportion of coronary patients, including those treated with revascularization, does not achieve the lifestyle, risk factor and therapeutic targets for the prevention of cardiovascular disease.

This is one of the reasons why the CR can be really beneficial after PCI.

CAUSES OF LOW RATE OF CARDIAC REHABILITATION AFTER PCI

The percentage of eligible subjects enrolled in cardiac rehabilitation program, in Europe, ranges from 3% to 90%^[15]. As a final result less than half of the subjects suffering from coronary artery disease can access this treatment. Routinely only some groups of patients, post myocardial infarction (MI) and CABG, are admitted to CR but others like PCI are neglected. In Italy only 4% of the patients after PCI undergoes CR, instead of 75% of CABG and 16% post-MI^[16]. In more recent studies^[17,18] by two-thirds to one-third of the PCI are not referred for CR. Furthermore lower is CR uptake after elective PCI as compared to acute PCI, especially for ST-elevation MI. Other factors associated with decreased referral are female gender, older age, non-Caucasians, illiteracy comorbidities especially diabetes and peripheral artery disease, lack of insurance and larger distance to the hospital.

Other causes, closely related to the procedure itself, may contribute to explain the low referral rates. First the short hospital stay^[19], limits the opportunities for inpatient education, the minimally invasive nature of the procedure may explain the lack of motivation for the patients in lifestyle changes. In addition, the patients that experiments the rapid improvement of symptoms may believe to have been "permanently" cured^[20]. Then, the youngest age of the patients in comparison to those undergone CABG, the better muscular function and well-being with rapid return to the working activity are other factors that induce to believe to have been cured of by the PCI and therefore, to be to low risk of relapsing of CAD.

The professional barriers, i.e., the lack of awareness and knowledge of the benefits of CR, from physicians and health care providers are the main factor that hinders the refer the patient after PCI, to a program of CR. The excessive distance from the hospital, the inadequate remuneration, the poor knowledge of the programs by the patients, the overreliance on physicians judgement that patients are not likely to participate (underestimating the role of the nurse), are other factors that significantly reduce the participation in the CR^[21].



Often the interventional cardiologist, whose vision of the ischemic heart disease is “stenosis-based”, strengthens this belief. Each narrowed coronary arteries should be dilated without assessing the induced ischemia (with the stress testing or fractional flow reserve) thinking that this will result in a sure improvement of the symptoms, prognosis and of the psychological and physical state. As a result the number of PCI is high and that of patients admitted to CR still low.

Instead, a combined strategy of automatic reference at the patient discharge, associated with a motivational interview has been shown to have high rates of enrollment and be able to increase by 45% the number of cardiac patients able to access the CR^[22]. Is crucial, that the appointment for CR orientation, will occur early, within 7-10 days after PCI discharge^[23].

PERSISTENCE OF CORONARY RISK FACTORS AND IMPACT ON THE FOLLOW-UP

The profile risk factor profile, of subjects undergoing PCI may be worse^[24] than those of other cardiac patients and, anyway, is underestimated by both the patient and physician. The non-adherence to a rehabilitation program is associated, more frequently, to the persistence of inappropriate dietary and life style behaviours, as well as risk factors.

It is definitely known that the progression of coronary artery disease, facilitated by the persistence of risk factors, it may offset the benefits that surgical and mechanical revascularization.

The decline of the mortality for coronary heart disease in the last 20 years in UK is due above all to the reduction of the principal factors of risk, especially smoking; the impact of the CABG realizes the 3% of such reduction and the angioplasty only the 0.8%^[25]. The adoption of the IMPACT mortality model, not surprisingly showed the same results in other nations such as the USA^[26], Italy^[27], Portugal^[28] and in several other countries. The data are in perfect agreement with the INTERHEART study. This emphasizes the importance of a comprehensive strategy that promotes reductions in major risk factors and that maximizes, for secondary prevention, population coverage of effective treatments.

The BARY study^[29] assessed the damage of myocardial perfusion due to failure of revascularization versus progression of native disease in PCI and CABG. Native coronary artery disease progression occurred more often than failed revascularization in both PCI and CABG-treated patients as a cause of jeopardized myocardium (analysed as distribution of coronary vessels and stenosis) and angina recurrence; the prevalence of angina was higher at five years in PCI vs. CABG (28% vs. 18%; $p < 0.03$). Approximately 6% of patients after PCI will require, at one year follow-up, a new procedure of non target-lesion (TL) progression^[30]. The risk is higher in multivessel patients: the greater the atherosclerotic burden, the greater the progression of the disease.

Also in the drug-eluting stent era^[31], half of the unplanned revascularization at one year (12%) is due to non TL progression. Since the higher risk of revascularization of the culprit lesion is between 2 to 9 months and the risk of unplanned non-TL revascularization is constant over time, the progression of the disease is the main determinant of the risk of further events during the long term follow-up.

EFFECTS OF CARDIAC REHABILITATION AFTER ACUTE CORONARY SYNDROME

Several studies^[32-34] have demonstrated a reduction in mortality

and reinfarction after CR. The benefit is extended also to the risk of all-cause hospitalization and cardiac hospitalization especially among those coronary artery disease patients who complete the CR program^[35]. The consolidated positive effects were also confirmed by a meta-analysis^[36,37] showing a 20% reduction in all-cause mortality, minus 25% in cardiovascular mortality and about 20% reduction in the risk of AMI and PCI.

Was also demonstrated a dose response relationship between CR attendance and positive effect on follow up after AMI^[35,38]. More the number of CR sessions, mote the positive long-term outcomes. In a sample of 5% of the Medicare beneficiaries, attending all 36 sessions reimbursed was associated with a lower risk of death and myocardial infarction 4 years compared to attending fewer sessions with a linear extension ratio between number of sessions and benefit (Figure 2).

In addition, the reduction in mortality from all causes, in a heterogeneous population (after AMI, PCI and CABG) was demonstrated until to a long-term follow-up of 14 years, even if the dose response relationship was present only with smoking cessation^[39].

Therefore a PCI not followed from comprehensive rehabilitation programmes including exercise training, behavioural changes, education, psychological support, and optimized drug therapy will have a poor impact on recurrent events and long term prognosis of the patient.

CARDIAC REHABILITATION AFTER PCI: EFFECTS ON RISK PROFILE, EVENTS AND MORTALITY

There are several evidences that the CR has an effect on risk profile of the patient after PCI.

A study of the Duke University^[40] was one of the first to assess the impact of CR on patient functional outcomes after CABG and PCI. The authors show an improvement in physical function associated with CR (64% vs. 13%, $p < 0.001$). The subgroup analysis stresses that this improvement tends to be greater in younger than older ones, in men than in women and after CABG than after PCI. The greater damage of the physical function after cardiac surgery (due to the sternotomy with impaired function of the chest wall, anaemia, postoperative pain) results in greater gains in patients with CABG.

Besides, CR was associated with positive effects on healthy lifestyle for risk-factor counselling. We also evaluated^[41] the effects of CR on the coronary risk factors in patients that followed a long term program, managed together with the local coronary-club, for a period of 3-10 year after an acute coronary event. We demonstrated the reduction of BMI, smoking (from 44% to 4.4%) and the improvement of lipid levels (hypercholesterolemia from 55% to 20%); was also increased the time spent on physical activity with reduction of sedentary lifestyle. The phase 3-4 of CR is the winning strategy: a treatment for just 4 weeks, although residential has only a few behavioral effects (diet, physical activity), but does not affect the BMI, lipid levels, blood pressure and psychological profile and quality of life (QOL)^[42].

It's really important in PCI P to recognize the negative emotional response^[43] (due to anxiety and depression) because can inhibit physical activity after the procedure. This kind of response is more frequent in women that also were less physically active. Also a Home-based program of individualized CR^[44], combining physical exercise to control of the factors and psychosocial counselling improves risk factor profile and work resumption after PCI.

Not only this approach is effective, but also cost-effectiveness. In

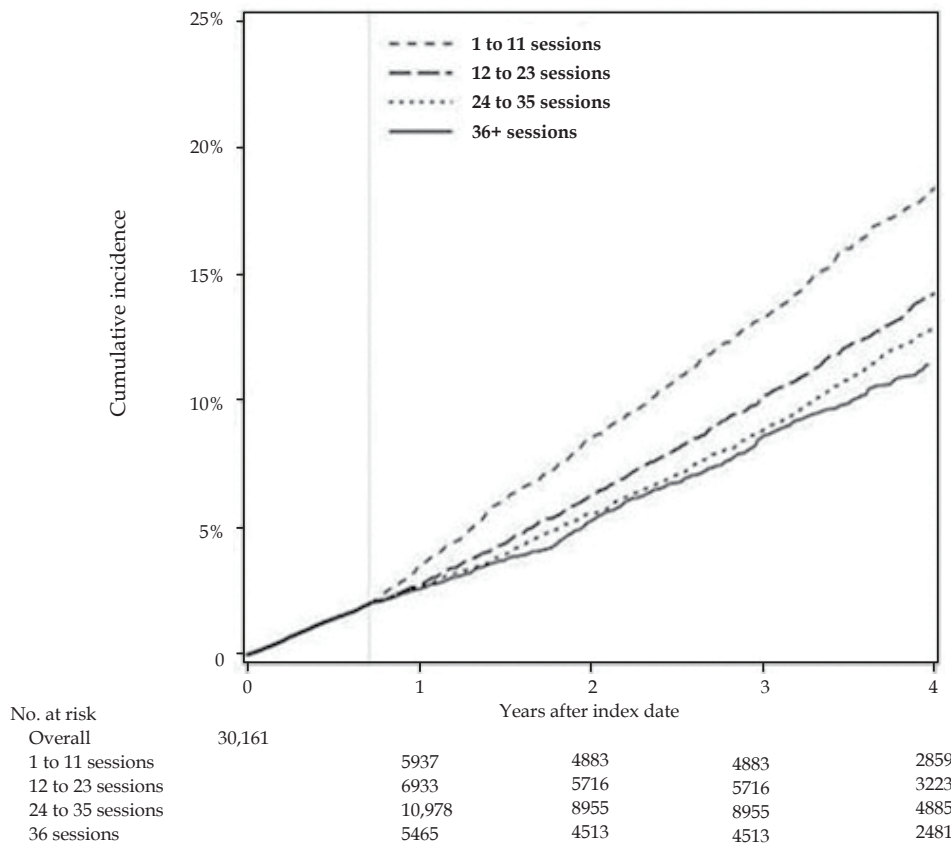


Figure 2 Cumulative incidence of death by number of cardiac rehabilitation session attended. *Source: Hammill B G et al. Circulation 2010; 121: 63-70.*

a short course (8 week) of CR ad prevention program, prospective randomized controlled trial^[45] patients, with recent AMI or after elective PCI, were less anxious and depressed, with improvement of QOL. The cost utility calculated was 640 dollars saved per QALY (quality-adjusted life-year gained) gained. This saving was due above all to the reduction of the procedures of re-PCI (13% vs 26% $p < 0.05$).

In a small study^[46] patients, recently submitted to PCI, were randomize to an aggressive treatment to fight the usual risk factors (smoke, diet, exercise and stress) or to the usual care: the life style changes were present until a 60 month follow-up and were associated to a significantly lower rates of events (AMI, CABG, re-PCI, cardiac death: 30.4% vs 53.7%) and cardiovascular mortality (2.2% vs 14.6%). Also in the subset of AMI treated with primary angioplasty^[47,48], the incidence of restenosis, angina pectoris with resulting reintervention, all revascularisations, and death was significantly lower when PCI patients are included in a CR program.

The effect of CR is manifested on the stabilization and likely regression of coronary atherosclerotic lesions, rather than on restenosis of the CL. In addition, it is also enhanced its collateral circulation. In the ETICA trial^[49], the angiographic restenosis rate was unaffected by exercise, but in patients with restenosis thallium uptake improved only when undergone exercise sessions 3 time a week at level of 60% of VO_2 max. Therefore exercise is able improve myocardial perfusion independently from the stenosis's degree. Moreover trained patients had a lower progression of CAD than untrained controls at follow-up angiography (7.6% vs 25%, $p < 0.03$).

Exercise training treats the entire coronary vasculature, not just the area subjected to the PCI, and progression of other lesions also contributes to recurrent events and mortality after angioplasty. Moreover, high intensity and interval training exercise may contribute to the beneficial effect of exercise on restenosis, reducing the level of

C-reactive protein^[50] and other markers^[51] of inflammation. Recently a not randomized and small-sized study^[52], showed that regular exercise can reduce the at 9 months follow-up angiography, the late luminal loss in the stented coronary segment in AMI patients together with a significant increase of HDL-C level.

The therapeutic adherence is an important factor in explaining the efficacy of CR. The Italian ICAROS survey^[53], a multicenter, prospective, longitudinal one-year survey of patients on completion of a CR program, after CABG and PCI, showed an excellent prescription, modification and adherence (documented from Morisky score equal to or greater than 3 in 90.8%) of cardioprotective drugs. The prescription rate were, at the end of CR program were: 86.3% statins, 80.8% beta-blockers and 77.7% Ace-inhibitors. The achievement of the right dose for these cardiac drugs, is essential for secondary prevention as demonstrated by the level of LDL-C at target in 69.3% of subjects.

Finally, a recent large study^[54] has shown the efficacy of the CR after PCI also on mortality. A retrospective analysis of data from a prospectively collected registry of 2395 consecutive patients demonstrated a reduction in all-cause mortality of about 30%. A trend toward decreased cardiac mortality was also observed and a neutral effect on recurrent MI and revascularization. Also a dose response relationship was not present, but the patients undergone on average, only 13 sessions (Figure3).

The differences, for myocardial revascularization and reinfarction, compared to previous studies^[35,38] on CR post-AMI (including more CABG patients), may be attributable to more stringent monitoring after PCI and that the effects of CR in PCI patients result in a shift from fatal to nonfatal events.

The rehabilitation program can be done safely also in patients with incomplete revascularization^[55]. The researchers, clinicians, and



policy-makers should focus on evidence of CR effectiveness after PCI, increasing the number of patients (now not more than 40%^[54] under the best conditions) participating in these programs.

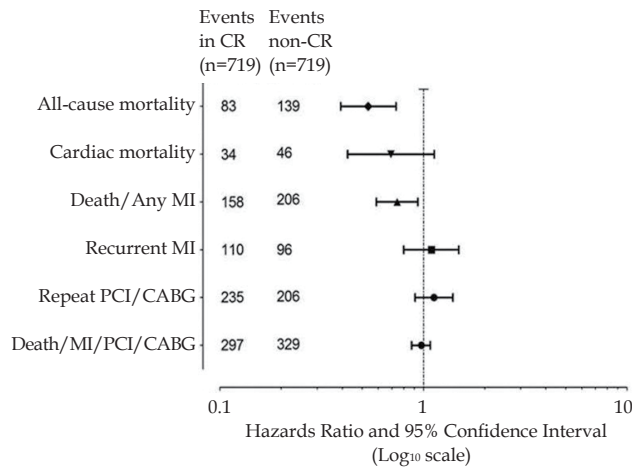


Figure 3 Association between cardiac rehabilitation (CR) participation and mortality in the propensity score-matched group. Source: Goel K *et al.* *Circulation* 2011; 123: 2344-2352.

CARDIAC REHABILITATION AFTER PCI: ONLY HOSPITAL-BASED?

The Home-based CR can be a valuable tool to counteract the low participation in the programs of CR. The system barriers^[56,57], such as the accessibility of the clinic, the distance from the patient's home, and the heavy traffic or the difficult parking are exceeded from home-based CR. In addition, the Home-base is effective, in terms of functional capacity^[58], as the hospital-based CR, not exposing the patients to major exercise-related adverse events^[59].

This kind of CR is able to improve the total work capacity and the quality of life, even in older patients, with a cost/effectiveness ratio better than the hospital-based CR^[13]. Furthermore, the effects on lifestyle seem to be more durable for the educational action of self-management of the exercise program. In patients following PCI, a home based CR program improves work resumption patterns and adherence to drug therapy^[44,60]. The Telecardiology can be useful not only to improve adherence and functional capacity, but also to reduce the risks of home-based CR^[61].

Two systematic reviews and meta-analysis^[62,63] show that after myocardial infarction or revascularization there are no differences between the two ways of CR, in terms of mortality, events in the follow-up, exercise capacity, quality of life and modifiable risk factors (hypertension, dyslipidemia, smoking). Also as regards the health care cost, there is absence of evidence of differences, but there is a trend to a better adherence, with the home-based CR^[63].

The unsupervised/home rehabilitation represents however a valid alternative to the hospital training, if the prescription of the physical activity is preceded by a suitable program of education to the self-management and by a complete evaluation of the risk category of the patients, avoiding the high risk.

To achieve the best results with the Home-based CR is desirable that the first sessions (4-8) of the CR program are supervised in hospital^[13,60]. So the patients acquires the notions of the correct execution of the exercise and learns the main precautions. A periodic evaluation, made by physiotherapist or CR-nurse, will be useful to adjust, if necessary, the exercise prescription and to enhance adherence with intervention^[13,60]. Finally, also these patients must

access to the programs of correction of the coronary risk factors, psychological and social support and educational reinforcement, bases of the *Comprehensive CR*.

The preference of the patients should therefore be considered when choosing between traditional hospital and home-based CR.

CARDIAC REHABILITATION: ONLY AFTER PCI?

During acute coronary syndrome the role of aggressive treatment and percutaneous revascularization is well defined. The same can not be said in the case of stable angina pectoris. In the cornerstone study of Hambrecht and colleagues^[64], 101 men with stable angina were randomized to exercise training (20 minutes of bicycle ergometry per day) or PCI. Exclusion criteria were: high-grade left anterior descending lesion, >25% left main stenosis, valvular disease, an ejection fraction<40%, an AMI within 2 months, or a revascularization procedure within 12 months. Effort ECG and coronary angiography were repeated after one year. Atherosclerosis progression (angiographic score), was significantly reduced in the exercise-trained group; while higher was the event-free survival (88% vs 70% in the PCI group, $P<0.02$) and also increased the maximal oxygen uptake (Figure 4). In addition to providing clinically superior outcomes, the cost of medical care over the year of the study for the exercise-trained subjects was 40% less (\$3708 vs \$6086) than that for the angioplasty patients

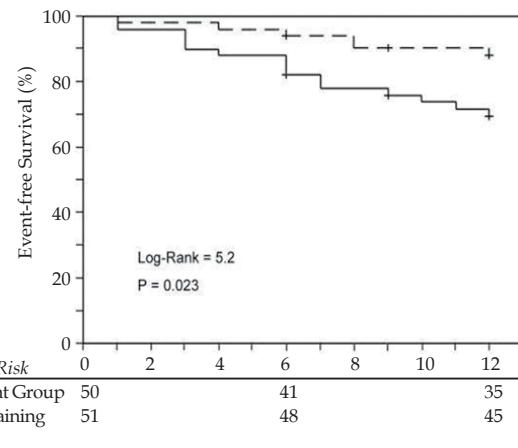


Figure 4 Event-free Survival after 12 months was significantly superior in training group versus PCI group. Hambrecht R *et al.* *Circulation* 2004; 109: 1371-1378.

Different meta-analysis before^[65] and after^[9,66] the use of DES comparing PCI to conservative optimal medical treatment in P with stable CAD the angioplasty did not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction. There was a trend for increased risk of AMI in patients undergoing PCI as better results of invasive approach in the proximities of AMI for the "old" meta-analysis^[65] and a greater angina relief for the new one^[66].

Anyhow, no benefit was found also in the subgroup of patients with stable coronary artery disease and strictly documented ischemia^[9,65]. The availability of more and more effective drugs (second-generation statins, dual antiplatelet therapy and new antiplatelets drugs); the physical training and CR programs have exceeded the progress of coronary artery devices, at least in the case of elective PCI. So it is probably true "that many percutaneous interventions that currently are performed in patients with non-acute CAD probably are not justified"^[65].

EXERCISE AFTER PCI: TIMING, SAFETY, PRESCRIPTION AND MECHANISM

Only one agent exists “with lipid-lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic and antidepressive qualities^[67]”: the exercise.

Anecdotal cases of thrombotic coronary occlusion associated with exercise testing^[68] have prompted some authors to exclude the feasibility and safety of early exercise in patients who underwent PCI^[69]. After MI (both STEMI and NSTEMI), the guidelines^[70,71] recommend a submaximal exercise test (ET) traditional at 3 to 5 days in patients without complications or a symptom-limited exercise test (done at 5 days or later) without stopping at a pre-specified target heart rate. Usually the symptom-limited maximal ET is performed at 14-21 days after the heart always using clinical judgement.

However generally the studies on early exercise testing^[72,73] after PCI have excluded patients undergone primary angioplasty in the fear to avoid the prothrombotic state exercise-induced. In the setting of stable coronary artery disease the execution of symptom-limited ET, even the day after PCI, was not associated with an increased risk of stent thrombosis. Of course a precocious ET can only be done after the procedure with radial approach.

A Japanese study^[74] was conducted on more than 13,500 patients after AMI, of which 4,360 after primary angioplasty with stenting in 31.9%. The timing for ET after stenting was 17 days, vs 13 days in patients after AMI ($p < 0.01$); also the maximal ET was slightly delayed (35 vs 27 days, $p < 0.05$). There was only one stent thrombosis (0-0.02%) in a P not treated with ticlopidine after maximal ET and no events in association with submaximal ET. A more recent study^[75] with the use of DES and Combined antiplatelet treatment (in 97.2% of the patients) confirmed the data. The subjects performed their first ET, before CR program, a median of 26 days after coronary stenting; 58% of them performed their first exercise test within 30 days after PCI. The CR was defined early when starting <1 month after PCI. The incidence of stent thrombosis was the same in the two groups of early and late CR (1.2/1.000 patients).

Therefore, the fear of stent thrombosis should not prevent the start of early CR following PCI, even if after AMI.

It's reasonable to perform a submaximal ET after a week from the procedure and after 14 days, for a maximal ET. If the primary PCI was due to a large AMI it is better to wait until 4 weeks. The CR can start immediately after the stress test in the case of stable coronary artery disease or acute coronary syndrome with minimal myocardial injury. In the case of Q-wave myocardial infarction is advisable to wait 1 month.

The exercise training program should include at least 150 minutes of activity, preferably 3-4 hours a week^[76]. Usually are performed 3-5 exercise sessions per week, for a minimum period of 4 weeks up to 24 with great variability from country to country^[74-76]. Our protocol provides for duration of 4-8 weeks depending on the degree of muscle conditioning, contractile function, age of the subject and the presence of comorbidities^[60]. The aerobic exercise training must be supervised and medically prescribed, at least in the early sessions and always in high-risk patients^[76] (heart failure, multiple risk factors, low ejection fraction, CR after primary PCI for a large AMI). Three bouts per week are the frequencies preferred, even for our experience, because allow reaching the maximum increase of VO₂ max.

patients must considered exercise prescription as pharmacological drug. Each session includes a warm up period of 5-10 min to allow gradual adaptation from rest to exercise; a cardiorespiratory exercise

period of 40 minutes and finish with a 5 to 10 minute cool down phase for a slow return to steady state condition of HR e BP. Session longer than 60 minutes do not improve VO₂ max and can increase the risk of incidents.

ECG monitoring is mandatory for the entire training program in patients with recurrent myocardial infarction, NYHA III, low threshold effort angina, ventricular tachycardia to load <6 METs and if SBP decreases during exercise. In other cases, it is reasonable to suspend ECG monitoring after 6-12 sessions^[77,78].

Two are the modality of training: endurance or interval training. The training program may differ between centers, but should include calisthenics and bicycle or treadmill exercises.

The endurance training is more used because allow the maximal increase of aerobic capacity; usually are chosen activities with dynamic component using cycloergometer or treadmill. In the later phases of the program isotonic exercises are integrated with resistance exercise (lifting weights). Indeed daily muscle activity is both static and dynamic. In low risk patient (stable angina, MI uncomplicated) showed that resistance exercise is safe and effective.

In “interval training” exercise and recovery periods succeed each other; the application of load for brief period, induce a better work adaptation in patient with effort angina and also in older, deconditioned subjects or with low EF. It is also mandatory in patients with peripheral arterial disease and intermittent claudication. Recently^[79] high intensity interval training exercise (as of 85-95% of peak HR) protocols have been shown to be safe in coronary heart disease patients with greater improvement in exercise capacity as measured by peak oxygen uptake.

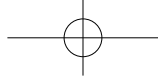
The intensity is the most important factor that influences the response to training. A level of exercise near the aerobic threshold induce the best “training effect”; a low level activity is below the 40% of VO₂ max, a medium at 40-60% and a high level above 60% of VO₂ max. Greater is the increase in aerobic capacity, greater is the cardio protective effects of the exercise^[80,81].

In clinical practice, the availability of ergospirometry is limited, so is used the maximum HR during the ET. During dynamic exercise involving large muscle group, a relatively linear relation exists between HR and oxygen uptake. The Target Heart Rate to be achieved during the exercise session is calculated as a percentage of peak HR during ET: 70-85% of the peak HR is the intensity level usually used. With the Karvonen method^[82], the results are similar, but the upper limit is slightly higher corresponding to about 90% of the peak HR (in the area of high intensity exercise). In case of therapy with beta-blockers we prefer to add, at the rest HR, the 70-85% of HR reserve.

As the P become familiar with the feeling associated with exercising, the need for an objective measurement of HR declines. However the self-measurement of pulse HR a must be encouraged and checked by nurse. Furthermore the Borg's Rate Perceived Exertion Scale^[83] can be used by to rate the intensity of an exercise.

The stress test is mandatory to set^[76] the workload either on bicycle ergometer, or on treadmill, with the calculation of the target heart rate derived from peak exercise capacity, but the physical training must be individualized according also to concomitant cardiac conditions (valvular disease, heart failure, low ejection fraction, atrial fibrillation), to the presence of comorbidities (osteoarticular diseases), to the age of the patient and to the degree of muscle deconditioning.

Trough repetitive increase of laminar shear stress^[84], exercise leads to an increase of NO-bioavailability as result of an activity of the endothelial nitric oxide synthase (eNOS). Nitric oxide is responsible for vasodilation and increasing perfusion. HDL is able to modulate



eNOS activity; this activation is impaired in CAD P and is restored by exercise^[85]. Moreover the exercise, by a reduced production of the reactive oxygen species^[84] (ROS) leads to a reduced inactivation of NO: the final result is an increase in the bioavailability of NO^[86].

Again via the activity of eNOS, the exercise is able to mobilize mesenchymal stem cells and endothelial progenitor cells, bone marrow, so as to restore the integrity of the endothelium damaged in atherosclerosis^[85]. The reduction of arterial stiffness and modulation of microRNAs are other possible positive benefits of the exercise^[86].

Finally, as already surmised by other studies^[49], exercise can stimulate the growth of collateral circulation. After a 3-month endurance exercise training program, in the vessel initially undergoing PCI, there was an increase in collateral flow index, a marker of collateral circulation. Furthermore this is correlated with the performance (VO₂max) evaluated at bicycle spiroergometry^[87].

Besides these molecular mechanisms, well known are the effects on plasma lipids, insulin sensitivity, inflammation, and blood pressure.

CONCLUSIONS

The transition from the “intervention” to the “prevention” phase of Cardiology is mandatory. The good results of the percutaneous revascularization therapy of the coronary heart diseases must be consolidated and optimized with a comprehensive CR.

The promotion and maintenance of good health is achieved through a multi-step process that only CR allows to complete: risk assessment, optimization of drug therapy, exercise, educational programs, psychological support, and follow-up with possible actions for reinforcement. The CR allows not only to improve functional capacity, promote a healthy lifestyle and improve the risk profile, but above all it is able to significantly reduce the recurrent events and all-cause mortality. Besides is a highly cost-effectiveness treatment.

The physicians, health service providers, policy makers who deal with health care policy can not be separated from the implementation of CR in modern evidence-based cardiac therapy. It's time to be as aggressive with prevention as we were with intervention^[88].

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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Peer reviewer: Francesco Giallauria, MD, PhD, Department of Translational Medical Sciences, Cardiac Rehabilitation Unit, University of Naples "Federico II", Via S. Pansini 5, 80131, Naples, Italy.