Comparison of the improvement of flow-mediated dilatation in patients with acute coronary syndrome versus stable angina after six-month cardiac rehabilitation

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Abstract

Background: We investigated whether the improvement in endothelial function, measured using flow-mediated dilatation (FMD), an important predictor of cardiovascular outcomes, was comparable in acute coronary syndrome (ACS) versus stable angina patients after percutaneous coronary intervention (PCI) and a six-month cardiac rehabilitation (CR) programme.

Methods: We analysed the results from 119 patients who completed a six-month CR programme after successful PCI for stable angina (n = 50) and ACS (n = 69).

Results: After six months of CR, the results of FMD were significantly improved in both groups. There were no significant between-group differences in the FMD results at the six-month follow up.

Conclusion: After successful PCI and a six-month CR programme, FMD values were equally improved in both stable angina and ACS patients.

Keywords: coronary disease, exercise training, endothelial function

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Clinical results for cardiac rehabilitation (CR) for secondary prevention indicate that CR can reduce cardiovascular risk and event rates, foster healthy behaviours and promote active lifestyles.[1-5] The recent major evidence-based guidelines from the American Heart Association and the American College of Cardiology Foundation for the management and prevention of coronary heart disease provides a class 1 level recommendation for referral to a CR programme for patients with recent myocardial infarction (MI) or acute coronary syndrome (ACS). Referral to a CR programme is also recommended for patients with chronic stable angina, heart failure, and for patients after coronary artery bypass surgery or percutaneous coronary intervention (PCI).[2]

Impaired endothelium-dependent vasodilatation has been linked to the pathogenesis of atherosclerotic vascular disease. Endothelial dysfunction is an independent predictor of future cardiovascular events in patients with cardiovascular disease. The structural integrity of the endothelium is compromised in patients with atherosclerosis. Endurance exercise training improves nitrous oxide (NO) activity, oxidative stress, inflammation and insulin resistance results.[6-8]

Both invasive and non-invasive methods have been used for the evaluation of endothelial function, and flow-mediated dilatation (FMD) is one of the accepted techniques used to assess endothelial function.[7,9,10] An abnormal FMD result is associated with an increased coronary event risk in patients with established coronary heart disease.[6,8,11] However, only a limited number of studies have been performed that evaluate the effects of CR on the endothelial function of patients after coronary revascularisation, and that compare the improvement in endothelial function in patients with ACS or stable angina.

We investigated whether the improvement in endothelial function, measured using FMD, was comparable in patients with ACS or stable angina after PCI and a six-month CR period.

Methods

This was a single-centre registry study involving 119 patients who had received CR after successful PCI for coronary artery disease from January 2014 to June 2015. Only the patients who had completed the planned CR programme after PCI were enrolled in this study. This study was approved by the local institutional review board.

Patients were excluded from the case series if they dropped out of the CR programme, or if they had a history of prior myocardial revascularisation, high degree of atrioventricular (AV) block, severe aortic stenosis, systolic blood pressure > 200 mmHg or diastolic blood pressure > 110 mmHg at rest, left

ventricular ejection fraction 30%, pericarditis, cardiomyopathy, ST-segment depression > 2 mm at rest, uncontrolled tachycardia, exercise-induced malignant ventricular arrhythmia, acute systemic illness, skeletal vascular disease, or acute metabolic disorders. Patients who refused to provide informed consent for the exercise programme were excluded from both groups.

Each patient completed a six-month CR programme that began with an out-patient CR session, which was held within two weeks of the index PCI. The exercise training programme and CR comprised two stages as follows: the first stage consisted of six weeks of prescribed supervised exercise and the second stage of community-based and self-managed exercise for the remaining 28 weeks. Patients were required to visit the cardiac rehabilitation clinic at least twice a month. The second stage could be extended to six months depending on medical judgement or at the patient's request.

Cardiorespiratory capacity was measured twice using a symptom-limited exercise-tolerance treadmill test (ETT). The measurements were performed before the commencement, and at the end of the first six weeks of supervised exercise training. The ETT was conducted on the first day that the patient visited the CR clinic after discharge, using a modified Bruce protocol: we measured oxygen uptake during peak exercise (VO_{2peak}), exercise time, resting heart rate (HR), peak HR, resting blood pressure (BP), peak BP, rate pressure product (RPP), peak respiratory exchange ratio (RER: the ratio of VCO_2 over VO_2; the magnitude of the peak RER roughly reflects the effort expended by the patient at peak exercise), and the rate of perceived exertion (RPE). The exercise test was supervised by experienced physicians.

A real-time recording 12-channel electrocardiograph (Q4500; Quinton Instrument Co, Boston, MA, USA), respiratory gas analyser TrueOne 2400 metabolic measurement system (Parvo Medics Inc, East Sandy, UT, USA), an automatic blood pressure and pulse monitor Model 412 (Quinton Instrument Co), and a treadmill MedTrack ST55 (Quinton Instrument Co) were used for the ETT.

All tests were terminated according to the American Heart Association (AHA) termination criteria and the patients were instructed about the termination of the ETT before the test. When the test was close to the end, patients were encouraged to endure the test and to stop only when experiencing intolerable dyspnoea, unless there was an event that met the ETT termination criteria in the AHA guidelines.

The patients initially participated in six weeks of prescribed, supervised exercise. Exercise intensities of 40 and 85% HR reserve were calculated using the Karvonen formula: [(maximal HR – resting HR × % intensity) + resting HR], based on the results obtained during the first ETT.

The CR programme was composed of 10 minutes of warm up (stretching), 40 minutes of main aerobic exercise, and 10 minutes of cool down, three times a week for six weeks, for a total of 18 sessions. Following the completion of the six-week CR programme, the ETT was performed again. The VO_{2peak}, ETT time, resting HR, peak HR, resting BP, peak BP, RER, RPP and RPE were measured again during the second ETT.

After the six-week supervised exercise period, the community-based, self-managed exercise was performed based on the results of the reassessed cardiorespiratory capacity for the remaining period. The patients were required to exercise at a local fitness centre and maintain aerobic exercise on a treadmill or bicycle ergometer. Every exercise training session was required to be one hour in length and was to be performed three times per week.

The FMD was measured within two weeks of the PCI, and was followed up at six months after the initiation of the CR programme. Endothelial function (endothelium-dependent brachial artery FMD) was measured as previously described.[10,12,13] Briefly, each patient arrived at the laboratory at a similar time of day (8:00–9:00). Patients were required to fast, avoid exercise and smoking, and to avoid consumption of alcohol or anti-oxidant vitamins, for at least 12 hours before the test.

The FMD was measured by a single ultrasonographer who was blinded to the subject's clinical status. After a 10-minute equilibration period, the measurement was taken in the right arm while the patient was in the recumbent position in a temperature-controlled room (22°C). Using an 11–3-MHz linear array (L11-3) transducer connected to a Philips iE33 (Philips Medical Systems, Andover, MA, USA) echocardiography machine, the brachial artery was longitudinally imaged approximately 5 cm proximal to the antecubital crease, at the point at which the clearest image was visible. The skin surface was marked when a reasonable image was obtained. The arm and the ultrasound probe were kept in the same position by the ultrasonographer throughout the study.

A pneumatic cuff was placed distal to the imaged artery, and baseline scans for the assessment of the resting vessel diameter and flow were recorded. The occluding cuff was then inflated to > 50 mm Hg above the systolic blood pressure value for five minutes, and the diameter was measured 30 seconds before cuff deflation. After deflation, the arterial diameter was measured at 60 and 90 seconds in order to determine the maximum post-occlusive reactive hyperaemia diameter. An electrocardiogram was monitored continuously and blood pressure was recorded each minute in the left arm throughout the test.

Statistical analysis

Depending on the distribution, the data are expressed as mean and standard deviation (SD) values or as median values with interquartile ranges. Categorical variables were compared using the χ^2 test. Continuous variable data were compared within groups using the paired Student's *t*-test, and between groups using the unpaired Student's *t*-test. A two-tailed *p*-value < 0.05 was considered to indicate a statistically significant result. All clinical and laboratory data were analysed using SPSS software (version 25.0).

Results

Of the 119 patients, 69 presented with ACS and 50 with stable angina. Table 1 presents a summary of the results of the subjects' clinical characteristics. The mean age of the patients was 54.9 ± 9.1 years, and the patients in the ACS group were slightly younger than those in the stable-angina group (52.9 ± 9.1 vs 57.6 ± 8.5 years, respectively, $p = 0.050$). There were no between-group differences in the distributions of males, hypertension, diabetes, dyslipidaemia or smoking. A greater percentage of patients in the ACS group took angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), and beta-blockers, compared to the stable-angina group patients. All the patients in both groups received statin and dual anti-platelet therapy.

Table 1. Baseline characteristics by clinical presentation

Variables	*Total* (n = *119*)	*Stable angina* (n = *50*)	*ACS* (n = *69*)	p-*value*
Age (years)	54. 9 ± 9.1	57.6 ± 8.5	52.9 ± 9.1	0.050
Male, *n* (%)	104 (87.4)	41 (82.0)	63 (91.3)	0.131
BMI (kg/m²)	24.9 ± 2.6	24.9 ± 2.5	24.9 ± 2.7	0.887
Hypertension, *n* (%)	38 (31.9)	19 (16.0)	19 (22.0)	0.227
Diabetes, *n* (%)	36 (30.3)	15 (30.0)	21 (30.4)	0.959
Dyslipidaemia, *n* (%)	39 (32.8)	16(32.0)	23 (33.3)	0.878
Current smoker, *n* (%)	55 (46.2)	18 (36.0)	37 (53.6)	0.057
Medication				
ACEI/ARB, *n* (%)	71 (59.7)	23 (46.0)	48 (69.6)	0.010
β-blockers, *n* (%)	85 (71.4)	29 (58.0)	56 (81.2)	0.006
Calcium antagonist, *n* (%)	21 (17.6)	16 (32.0)	5 (7.2)	< 0.001
Nitrate, *n* (%)	72 (60.5)	27 (54.0)	45 (65.2)	0.086
SBP (mmHg)	119.9 ± 12.1	121.8 ± 10.6	118.5 ± 12.9	0.145
DBP (mmHg)	70.3 ± 13.4	71.8 ± 12.4	69.2 ± 14.2	0.304
Heart rate (beat/min)	65.8 ± 8.9	63.9 ± 8.0	67.1 ± 9.4	0.069

Data are expressed as numbers (%) and means ± SD. ACS, acute coronary syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

The FMD results at baseline and at six months after the initiation of CR are presented in Table 2 and Fig. 1. At baseline, the FMD values were lower in the patients with ACS than in those with stable angina, but the mean difference was not statistically significant (7.6 vs 8.2%, respectively, p = 0.180) (Table 2) (Fig. 1). However, after six months of CR, the FMD was significantly improved in both groups (1.3% increase in the ACS group and 1.0% increase in the stable-angina group, p = 0.002). There were no significant differences in the FMD results at the six-month follow up in the patients with ACS compared to the patients with stable angina (9.2 vs 8.9%, respectively, p = 0.61).

The results for cardiopulmonary exercise testing and the echocardiographic parameters are presented in Table 2. The results for the VO_{2max}, maximal metabolic equivalent (MMET), maximal respiratory exchange ratio (max RER) and exercise duration were similar in both groups. After the six-month CR programme, the VO_{2max} was improved in both groups (Table 2) (Fig. 2); the VO_{2max} increased 2.1 ml/kg/min (0.8–3.4, p = 0.003) more in patients with stable angina and 2.6 ml/kg/min (1.1–4.2, p < 0.001) more in ACS patients at six months compared to the baseline value of each group. The baseline left ventricular (LV) systolic function was better in the stable-angina patients compared to the ACS patients (59.4 ± 10.2 vs 43.6 ± 13.3%, respectively, p < 0.001). Additionally, a greater improvement in LV systolic function occurred in the ACS group compared to the stable-angina group, although the difference was not statistically significant.

The results for the changes in biochemical parameters after the end of the CR programme period are presented in Table 3.

Table 2. Changes in FMD, cardiopulmonary exercise testing and echocardiographic parameter results after a CR programme

	Total		*Stable angina*		*ACS*	
Parameters	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
FMD (%)	7.9 ± 2.6	9.0 ± 2.3**	8.2 ± 2.7	9.2 ± 2.1*	7.6 ± 2.5	8.9 ± 2.4*
Exercise duration (min)	15.3 ± 2.6	16.0 ± 2.7	15.0 ± 2.5	16.3 ± 2.1**	15.4 ± 2.7	15.8 ± 3.0
MMET	8.3 ± 1.9	9.1 ± 2.2**	8.2 ± 2.0	8.8 ± 1.9*	8.5 ± 1.8	9.3 ± 2.4**
Max RER	1.1 ± 0.1	1.2 ± 0.1*	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1*
VO_{2max} (ml/kg/min)	29.2 ± 6.6	31.9 ± 7.9**	28.6 ± 6.9	30.9 ± 6.7**	29.6 ± 6.4	32.5 ± 8.5**
LVEF (%)	48.7 ± 21.1	49.7 ± 19.6	59.4 ± 10.2	59.9 ± 13.7	43.6 ± 13.3‡	46.2 ± 16.3‡

Data are expressed as numbers (%) and means ± SD. ACS, acute coronary syndrome; FMD, flow-mediated dilatation; LVEF, left ventricular ejection fraction; max RER, maximal respiratory exchange ratio; MMET, maximal metabolic equivalent.
Baseline versus six months; *p < 0.05, **p < 0.01, stable angina versus ACS; †p < 0.05, ‡p < 0.01.

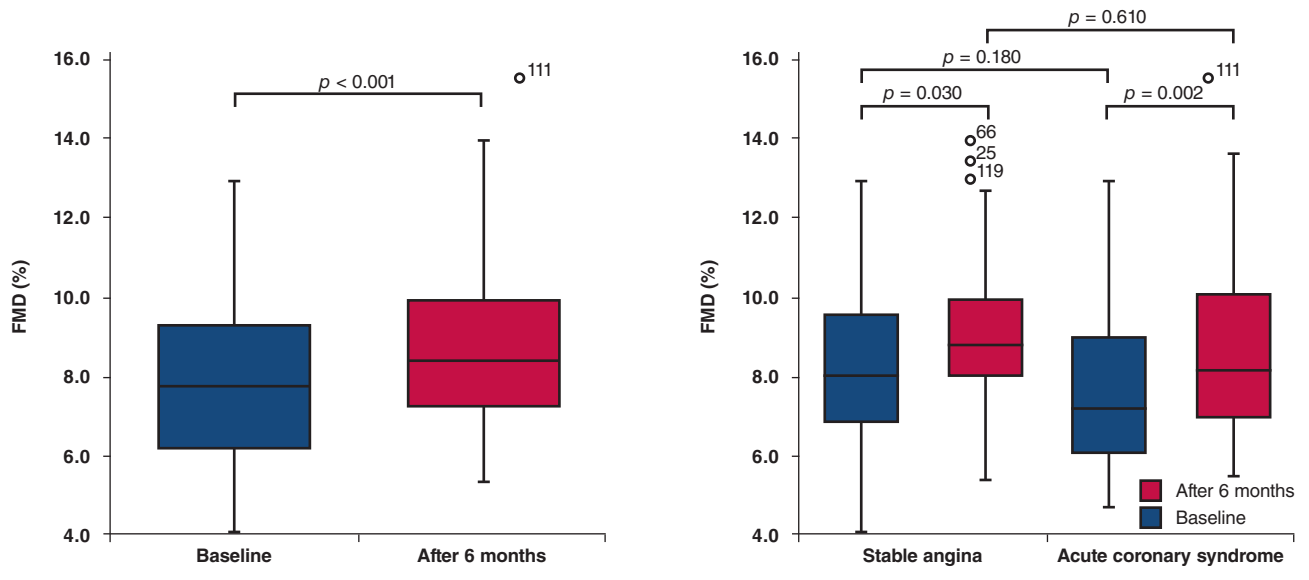

Fig. 1. Changes in FMD before and after a six-month CR programme. A. All patients. B. Patients with stable angina versus ACS.

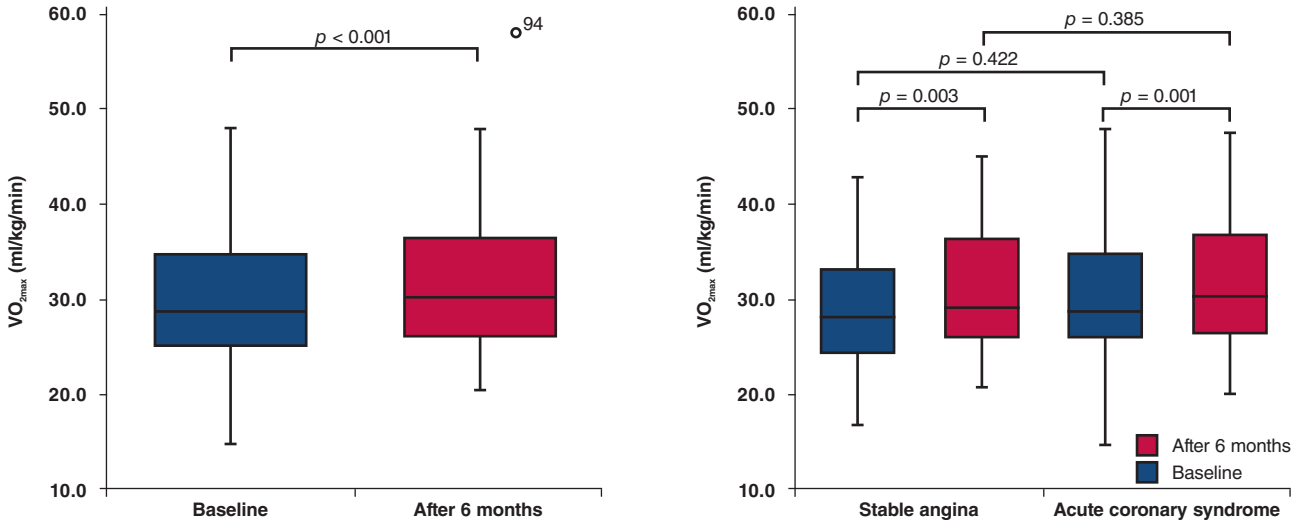

Fig. 2. Changes of VO_{2max} before and after a six-month CR programme. A. All patients. B. Patients with stable angina versus ACS.

The mean concentration of high-sensitivity C-reactive protein (hs-CRP) at baseline was significantly higher in the ACS group than in the stable-angina group (1.21 ± 3.73 vs 0.49 ± 1.46 mg/dl, respectively, $p = 0.023$). However, six months after the initiation of the CR programme, the mean hs-CRP concentration was significantly decreased in both groups and was not significantly different between groups (0.21 ± 0.39 vs 0.24 ± 0.49 mg/dl, respectively, $p = 0.989$). The target goal for the mean low-density lipoprotein (LDL) cholesterol concentration (88.0 ± 28.5 mg/dl; 2.28 ± 0.74 mmol/l) for the ACS group was not reached despite efforts, such as high-intensity statin therapy, used to control it.

Discussion

In this study we showed that endothelial function, measured by FMD, was improved in patients with coronary artery disease who underwent PCI, regardless of ACS or stable angina after a six-month CR programme. However, there was no significant difference in the improvement of the FMD values between the two groups. The ACS patients tended to have lower FMD values before CR, compared to the patients with stable angina.

Endothelial function is an 'excellent barometer' of vascular health and can be used to gauge cardiovascular risk.[9] A pathogenic link between coronary endothelial dysfunction and cardiovascular events was found almost simultaneously by Suwaidi *et al.*[11] and Schächinger *et al.*[8] The FMD result reflects the relaxation of a conduit artery when it is exposed to increased flow and increased shear stress.[14]

Numerous studies have documented the various effects of cardiac rehabilitation on cardiovascular disease. In 2004, Hambrecht *et al.* reported that when patients with stable coronary artery disease participated in a 12-month programme of regular physical exercise, they had superior event-free survival and exercise capacity, and at lower cost, compared to patients treated with PCI.[15] Many investigators have used FMD to evaluate the post-CR improvement in endothelial function in patients with coronary heart disease. Morikawa *et al.* suggested that exercise training improves endothelial dysfunction in patients with coronary spastic angina, and they found a significant correlation between the reduction in attack frequency and the improvement in FMD.[4]

Recently, Ades *et al.* found that there was a dose–response relationship between weight loss and endothelial-dependent FMD in patients with serious coronary heart disease who participated in a CR programme.[1] Weight loss and exercise in overweight patients resulted in a significant improvement in FMD. Their results suggested that the best predictor of the improvement in FMD is weight loss per se, rather than related measures, such as changes in fat mass, visceral fat, waist circumference or insulin sensitivity.[1] The initial mean body mass index (BMI) of their study population was 32.3 ± 4.1 kg/m^2, which was larger than that of our study population (24.9 ± 2.6 kg/m^2). However, we found that there was an improvement in FMD values after exercise training, even though most of the

Table 3. Changes in biochemical parameters after a CR programme

	Total		*Stable angina*		*ACS*	
Parameters	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
hs-CRP	0.87 ± 2.90	0.23 ± 0.44*	0.49 ± 1.46	0.21 ± 0.39*	1.21 ± 3.73†	0.24 ± 0.49*
HDL-C	42.4 ± 8.9	40.4 ± 8.0*	44.7 ± 8.9	41.8 ± 8.3*	40.7 ± 8.6†	39.4 ± 7.8*
LDL-C	116.9 ± 30.7	82.7 ± 24.7**	115.3 ± 31.2	74.3 ± 13.8**	118.2 ± 30.5	88.0 ± 28.5**‡
HbA_{1c} (%)	6.5 ± 1.5	6.5 ± 1.4	6.2 ± 1.1	5.7 ± 0.4	6.6 ± 1.7	6.8 ± 1.6

Data are expressed as numbers (%) and means ± SD. ACS, acute coronary syndrome; hs-CRP, high sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Baseline versus six months; *$p < 0.05$, **$p < 0.01$, stable angina versus ACS; †$p < 0.05$, ‡$p < 0.01$.

patients had a normal-weight BMI value. Therefore, our results are different from those of Ades *et al*. in that the endothelial function could be improved after exercise training, irrespective of the initial BMI value. A similar effect occurred in both of our patient groups.[1]

The high-density lipoprotein (HDL) cholesterol level might have decreased in both groups because we used high-intensity statin treatment to reduce LDL cholesterol levels. The change in the HDL cholesterol level was statistically significant, but decreased only by a small amount (2 mg/dl; 0.05 mmol/l). We do not suggest that this change was clinically significant and we should have applied more effort to reduce the LDL cholesterol level of the ACS group so that the target goal could be achieved.

The VO_{2max}, MMET, exercise duration and FMD results were improved at six months in each group, but there were no statistically significant between-group differences in these parameters. One reason for these results might be that the patients with severe heart failure [left ventricular ejection fraction (LVEF) 30%] were excluded from the ACS group.

Limitations

Our study had several limitations. First of all, we did not perform the comparison analysis between the patients who performed CR versus those who did not. Furthermore, this study was a retrospective study and we analysed registry data that included only patients who had received CR after PCI; therefore, the FMD data of patients who did not receive CR or PCI were unavailable. In addition, there was a significant difference in the patients' age and the use of ARBs or ACEIs; these differences were considered to affect atherosclerosis and endothelial function between the two groups. Despite these differences, the FMD values were improved in both groups when compared to the baseline, and this improvement was similar between the two groups. On the other hand, many previous studies have shown that cardiac rehabilitation has a benefit in improving endothelial function in patients with coronary events, and our study was performed based on these previous results.

Second, we measured FMD while the patients received standard medical treatment for ischaemic heart disease, including ARBs or ACEIs, beta-blockers and statins; these treatments could have affected the FMD results. However, we performed the examination under the same conditions for both groups, at baseline and six months after CR was initiated. Therefore, we suggest that the improvement in FMD after the six-month CR programme was independent of the drugs taken by the patients. Compared to other study populations, patients who had relatively less-serious disease could be enrolled in this study. Therefore, patients with unstable angina might have been included in the stable-angina patient group.

Third, except for seven ST-elevation myocardial infarction (STEMI) patients, PCI was performed via the subject's right arm, followed by measuring the FMD on the right arm within two weeks. In a recent study, Heiss *et al*. suggested that trans-radial catheterisation leads to dysfunction, not only of the radial artery, but also upstream of the brachial artery; they suggest that FMD should be interpreted with caution after trans-radial catheterisation.[16] Therefore, if we had measured FMD using the patients' left arm, we would have been able to see a little more clearly that the FMD improved.

Our study results did not suggest that there were improvements in LVEF as the FMD increased, especially in the ACS group. We also found no beneficial effect with regard to clinical outcome by improving the FMD result. The study duration was six months, which was a relatively short period of time. Patients with less-severe disease and a small number of patients were enrolled in the study. No major adverse cardiac event occurred during the six-month CR period. A long-term follow-up period of one year or more would be required to determine whether the improvements in FMD would affect the LVEF and clinical outcomes.

Conclusion

This study revealed that the FMD was equally improved after a successful PCI and a six-month CR programme for both ACS and stable-angina patients. The ACS patients tended to have a lower FMD before CR, compared to the patients with stable angina. Therefore, it is suggested that the endothelial function might be improved after planned CR in patients who received PCI, irrespective of whether they had ACS or stable angina.

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Telemonitoring may cut heart attack, stroke by 50%: five-year study

People enrolled in a pharmacist-led telemonitoring programme to control high blood pressure were about half as likely to have a heart attack or stroke compared to those who received routine primary care, according to research.

Researchers, led by study author Dr Karen L Margolis, executive director of research at HealthPartners Institute in Minneapolis, found that a heart attack, stroke, stent placement or heart failure hospitalisation occurred in 5.3% of the telemonitoring group versus 10.4% of the routine primary-care group.

'Home blood pressure monitoring linked with treatment actions from the healthcare team delivered remotely (telehealth support) in between office visits has been shown to lower blood pressure more than routine care, and patients really like it,' said Margolis. 'In addition, by avoiding serious cardiovascular events over five years, our results indicate significant cost savings.' Patients reported that they liked having support from a trusted professional, rapid feedback and adjustments to their treatment, and having someone to be accountable to.

Margolis reports that over five years, the savings from reduced cardiovascular disease events exceeded the telemonitoring intervention costs by $1 900 per patient. 'The findings were just short of statistical significance,' said Margolis, 'meaning they could have been due to chance. However, we were surprised that the figures on serious cardiovascular events pointed so strongly to a benefit of the telemonitoring intervention,' she said.

Uncontrolled high blood pressure is the largest modifiable risk factor contributing to death from all causes. Nearly half of US adults have high blood pressure, defined as equal to or greater than 130 mmHg systolic, or 80 mmHg diastolic. However, most adults with high blood pressure don't have their numbers under control.

Four hundred and fifty participants with uncontrolled high blood pressure were enrolled in the study, conducted at 16 primary-care clinics within the HealthPartners system in Minnesota. Participants were blinded and randomised to two groups: 222 patients were in the routine primary-care group, and 228 in the telemonitoring group that also received one year of remote care managed by a pharmacist. In the telemonitoring group, patients were able to measure their blood pressure at home and send it electronically to the pharmacist, who then worked with them to make medication and lifestyle changes in their treatment.

In clinic visits for all participants, researchers monitored blood pressure at enrolment, six months, 12 months, 18 months and five years; kept track of any heart attacks, strokes, coronary stents, heart failure hospitalisations and heart-related deaths that occurred; and counted all the costs of their blood pressure-related care and cardiovascular event care.

They found that in the telemonitoring group, there were 15 serious cardiovascular events (five non-fatal heart attacks, four non-fatal strokes, five heart failure hospitalisations, one cardiovascular death) among 10 patients. This group also had two stent placements, making the total event rate 5.3%.

In the routine primary-care group, there were 26 serious cardiovascular events (11 non-fatal heart attacks, 12 non-fatal strokes, three heart failure hospitalisations) among 19 patients. They also had 10 stent placements, making the total event rate 10.4%.

Based on these findings, 'widespread adoption of the telemonitoring model might help US adults with uncontrolled high blood pressure avoid serious cardiovascular events and reduce healthcare costs,' according to Margolis and colleagues. They recommend future studies to figure out how to increase the number of patients engaged in home blood pressure monitoring over many years, and to measure cardiovascular risk factors and cardiovascular events over that extended period.

The study's limitations are its relatively small size, and it was at a single medical group's urban and suburban primary-care clinics, which may not represent the diversity of patients who receive care in other settings across the country.

Source: *MedicalBrief* 2020