





Consensus Recommendations of the Asia Pacific Cardiometabolic Consortium on Secondary Prevention Strategies in Myocardial Infarction: Recommendations on Pharmacotherapy, Lifestyle Modification and Cardiac Rehabilitation

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Abstract

Secondary prevention of acute MI, both ST elevated and non-ST elevated is essential to reduce cardiovascular mortality and hospital readmission, ensuring patients return to normality with an improved quality of life. Thus far, professional associations and country-specific guidelines have provided guidance suited to their respective populations. The Asia Pacific Cardiometabolic Consortium has developed these consensus recommendations to unify the approach to long-term care of patients after MI, which can be applied across the Asia-Pacific region. The consensus statements, which were developed by an expert panel, took into account international and local guidelines and current evidence, along with the opinions and professional experience offered by regional experts. These statements were then put to an online vote to achieve a consensus. The resulting 13 statements discuss secondary prevention strategies encompassing pharmacotherapy, lifestyle modifications, cardiac rehabilitation and discharge management for the effective long-term care of patients with a history of type 1 MI, specifically relating to atherosclerotic plaque rupture and thrombosis.

Keywords

Asia-Pacific, cardiac rehabilitation, lifestyle modification, non-ST-elevated MI, pharmacotherapy, secondary prevention, ST-elevated MI

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The essential goal of secondary prevention in MI is to increase the survival of recovered patients by modifying risk factors to improve quality of life and to prevent recurrent coronary episodes. Patients with ST-elevation MI (STEMI) and non-ST elevation MI (NSTEMI) are at a high risk of recurrent MI, stroke and heart failure. Therefore, adherence to secondary prevention practices such as antiplatelet therapy, control of risk factors and cardiac rehabilitation is vital. Studies such as the EUROASPIRE I to IV surveys show that a vast number of patients with coronary artery disease (CAD) did not receive the secondary prevention measures laid down by international guidelines. In addition to the prevalence of smoking, lack of exercise and suboptimal diet, adherence to risk factor control measures and approved medication was poor. The fourth EUROASPIRE survey showed that, after a median time of 1.35 years following the last cardiac episode, 48.6% of recovered patients continued smoking, 66.6% of patients were physically inactive, and that

suboptimal blood pressure control (\geq 140/90 mmHg in 42.7% patients) and low-density lipoprotein cholesterol (LDL-C) levels (\geq 1.8 mmol/l in 80.5% of patients) were common. A systematic review and meta-analysis of more than 350,000 patients found poor adherence to medications for both primary and secondary prevention in patients with high cardiovascular risk during a median period of 2 years since the initiation of pharmacotherapy.

Lack of patient adherence to secondary preventive measures may be linked to demography, socioeconomic factors, lack of healthcare infrastructure to enable effective counselling, complex medication practices and lack of patient education.⁷ Further, secondary prevention settings vary between countries and are influenced by local and national regulations and patients' experiences of cardiac rehabilitation programnes.^{7,8} It is, therefore, important to specify a set of guidelines that

can be applied in a region–specific manner to effectively enable long-term care of patients with acute MI (AMI).

The INTERHEART study confirmed that risk factors for AMI are the same globally, regardless of income levels. 9 The Asia Pacific Cardiometabolic Consortium has developed a unified set of consensus recommendations with the help of a regional expert panel to address crucial strategies for the secondary preventive care of type 1 MI (occurring in those with atherosclerotic plaque rupture and thrombosis), in the Asia-Pacific region. These include strategies that can be effectively applied across countries in the region and are derived from existing international and regional guidelines combined with the professional experience and opinion of the experts on the panel.¹⁰⁻¹⁵ The strategies encompass pharmacology (antiplatelets, B-blockers, calcium channel blockers [CCB], reninangiotensin system blockers and lipid-lowering therapies), lifestyle modifications (smoking cessation, exercise and diet) and cardiac rehabilitation (patient assessment, physical activity counselling, exercise training, risk factor control, patient education, psychosocial management and vocational advice).

Confidence in consensus statements was based on the current level of evidence presented by meta-analysis with ≥100 subjects marked as 'strong', multiple studies alluding to the same result marked as 'moderate' and evidence from single studies marked as 'weak'. Confidence in consensus statements were evaluated by the experts using Grading of Recommendations Assessment, Development and Evaluation (GRADE) defined as: ¹⁶

- 1. High: authors have high confidence that the true effect is similar to the estimated effect.
- Moderate: authors believe that the true effect is probably close to the estimated effect.
- 3. Low: the true effect might be markedly different from the estimated effect
- Very low: the true effect is probably markedly different from the estimated effect.

Each author then cast an online vote to indicate their position on each statement, indicating whether they agree, were neutral or disagreed. A consensus was accepted as high when 80% of votes were agreed or neutral.

Pharmacotherapy for the Secondary Prevention of MI Antiplatelet Therapy

Statement 1. Indefinite use of aspirin in the dosage range of 75–162 mg/day is recommended for patients without contraindication after MI. In case of aspirin contraindication or intolerance, clopidogrel should be prescribed as a single long-term therapy.

Level of evidence: Strong Level of agreement: High

Aspirin inhibits thromboxane A2 of the cyclooxygenase pathway, preventing collagen-mediated platelet activation and aggregation.¹⁷ A meta-analysis of 15 randomised controlled trials (RCTs) confirmed aspirin's superiority over placebo in reducing the risk of MI, stroke and death from vascular events (OR 0.7; 95% CI [0.64–0.77]).¹¹ Across clinical practice quidelines, including those from the Asia-Pacific region, the indefinite

prescription of aspirin at a low maintenance dose is recommended in all patients with STEMI. $^{10-15}$ The expert panel recommends a long-term prescription of 75–162 mg/day of aspirin in STEMI patients who do not have aspirin-related contraindication or intolerance.

Aspirin sensitivity may manifest in certain STEMI patients with chronic rhinosinusitis or nasal polyps. Indefinite antiplatelet therapy with clopidogrel (300–600 mg loading dose followed by 75 mg/day for maintenance) is recommended for patients who cannot tolerate aspirin long-term by the National Institute of Health and Care Excellence in the UK, the Indian, the Japanese, and the Australia and New Zealand guidance. Interfect of the Capparate (ADP) with the P2Y receptor, interfering with platelet aggregation. Results from the CAPRIE trial comparing low doses of clopidogrel and aspirin showed that clopidogrel achieved better reduction in the combined risk of MI, systemic stroke and vascular mortality than aspirin, with comparable safety profiles. In the certain stroke and vascular mortality than aspirin, with comparable safety profiles.

Statement 2. Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) should be prescribed for up to 12 months in patients with acute coronary syndrome, irrespective of stent implantation. Recent data suggest stopping aspirin after 3 to 6 months after percutaneous coronary intervention (PCI) and continuation of a single antiplatelet agent. The use of prasugrel for up to 12 months should be confined to patients receiving PCI.

Level of evidence: Strong Level of agreement: High

The combined use of aspirin and a $P2Y_{12}$ inhibitor has an additive effect in inhibiting platelet activation, thereby reducing the risk of major adverse cardiovascular events in patients with STEMI. 20-22 Clopidogrel (75 mg/day), ticagrelor (120-180 mg/day) and prasugrel (3.75-10 mg/day) are the recommended $P2Y_{12}$ inhibitors for coadministration with aspirin (75–162 mg/day) in DAPT. The Australia and New Zealand guidelines and European guidelines recommend using the new generation P2Y₁₂ inhibitors ticagrelor and prasugrel over clopidogrel due to their superior risk reduction in mortality and recurrent $MI.^{10,11,15}$ In patients with very high bleeding risk, DAPT can be shortened to a duration of 6 months to reduce the risk of major bleeding without compromising efficacy against ischaemic events.²³ In patients with low bleeding risk but high risk of MI, for example after coronary stenting or in aspirin-related ischaemia, P2Y₁₂ inhibition for up to 3 years may be considered with either clopidogrel or ticagrelor. Further, DAPT for a duration less than 3 months should be considered for patients with high bleeding risk after drug-eluting stent implantation.¹⁴

The use of prasugrel should be limited to patients receiving PCI owing to the high intracranial bleeding risks associated with its use. ²⁴ In Japan and Taiwan, a reduced–dose regimen for prasugrel (20 mg loading dose and 3.75 mg daily dose) is recommended to factor in the high bleeding risk observed in these populations. The reduced prasugrel dosage was found to retain efficacy in MI patients by the PRASFIT-ACS trial conducted in Japan. ^{13,14,25}

Clopidogrel is recommended in triple therapy with an oral anticoagulant and in patients who cannot use prasugrel or ticagrelor as an adjunctive with fibrinolysis. The ATLAS ACS 2-TIMI 51 trial supported the addition of the direct oral anticoagulant rivaroxaban (2.5 mg twice daily) with aspirin

and clopidogrel.²⁶ The triple therapy reduced the composite endpoint of cardiovascular events, stroke and MI, along with all-cause mortality and stent thrombosis, over 13 months of observation. However, a threefold increase in intracranial bleeding and major bleeding was observed, cautioning the use of this triple therapy in patients with low bleeding risk.²⁶ The use of rivaroxaban with DAPT is not recommended in the Australia and New Zealand guidelines.¹¹

B-blockers

Statement 3. Treatment with β -blockers should be initiated in all patients post MI. Long-term administration of β -blockers to be considered in all patients with persistent angina, tachycardia, left ventricular dysfunction (ejection fraction <40%) or left ventricular failure.

Level of evidence: Strong Level of agreement: High

Statement 4. In cases of hypertension, tachycardia or angina, non-dihydropyridine CCBs may be used if β -receptor blockers are contraindicated.

Level of evidence: Weak Level of agreement: Moderate

β-blockers, such as carvedilol, bisoprolol, nebivolol and metoprolol improve cardiac output and left ventricular function while reducing peripheral vascular resistance, cardiovascular death and infarct size. A meta-analysis of 31 RCTs spanning 24,184 patients after an MI episode studied the effect of β-blockers (against placebo) on top of aspirin and lipid-lowering therapy. The efficacy of vasodilatory β-blockers was found to be specific to patients with reduced left ventricular function following MI in terms of reduction to all-cause mortality and recurrent MI. The CAPRICORN study revealed that carvedilol was efficacious in reducing all-cause mortality in patients with low left ventricular ejection fraction (LVEF) (≤40%), fibrinolysis or primary PCI reperfusion therapy.

The Indian and Taiwan guidelines state that every patient with STEMI should be started on a ß-blocker (unless contraindicated) as soon as haemodynamic stability is achieved; with the treatment continuing over 3 years. 12,14 The COMMIT/CCS-2 study, which observed patients on immediate IV metoprolol followed by an oral ß-blocker within 24 hours of MI onset showed reduced rates of MI and ventricular fibrillation in the metoprolol group but with higher rates of cardiogenic shock and no difference in mortality over placebo. 29 Haemodynamic stability is a prerequisite for treatment with ß-blockers.

Guidelines from India, Australia and New Zealand, Taiwan and Japan support the administration of oral β-blockers as an immediate step after an MI episode in patients without the complication of heart failure, low output state or an increased risk of cardiogenic shock. 11,13,14 The Australia and New Zealand. and Japan guidelines do not support the use of IV administration of β-blockers due to insufficient evidence of benefit in clinical studies. 11,14 There is also low evidence for the benefit of β-blockers in STEMI patients with normal cardiac function.

Data supporting the use of ß-blockers after MI predates early reperfusion therapy and shows benefit primarily in patients with large infarcts through reduced risk of rupture. More recent registries suggest modest benefits across patients with MI and support the early, but not long-term, use of

B-blockers. β-blocker therapy is contraindicated in cases of bradycardia, hypotension, bronchospasm, fatigue, reduced libido, depression and new-onset diabetes. In such cases, the India and Japan guidelines recommend the use of CCBs such as verapamil or diltiazem. However, CCBs should be avoided in the presence of left ventricular dysfunction or left ventricular failure. The CAMELOT study observing amlodipine (10 mg) against placebo or enalapril (10 mg) concluded superior efficacy of amlodipine in reducing cardiovascular events in patients with a history of MI. The efficacy of CCBs in Japanese subjects in the JBCMI study was comparable with β-blocker therapy in terms of the frequency of cardiovascular events during a follow-up period of 445 days.

Angiotensin-converting Enzyme Inhibitors

Statement 5. Long-term oral administration of angiotensin-converting enzyme inhibitors (ACEIs) is recommended for all patients post-MI and a must for those with reduced left ventricular function (≤40%), anterior MI, MI with left ventricular failure, diabetes or coexistent hypertension. Angiotensin receptor blockers (ARBs) may be used when ACEIs are contraindicated.

Level of evidence: Strong Level of agreement: High

ACEIs offer cardioprotection after MI by limiting infarct size and ventricular remodelling. These agents confer survival benefits independent of other therapies used in the long-term management of high-risk STEMI patients, such as aspirin or B-blockers, particularly for those who fall into subgroups of anterior MI, LVEF $\leq\!40\%$, heart failure, prior MI and tachycardia. Hence, all clinical guidelines recommend ACEIs in STEMI patients without contraindications. $^{10-15}$

A meta-analysis of the ACEI-based RCTs HOPE (ramipril against placebo), EUROPA (perindopril against placebo) and PEACE (trandolapril against placebo) found that long-term ACEI administration caused a significant reduction (p<0.0005) across all-cause mortality, cardiovascular mortality, non-fatal MI, stroke, heart failure, and a composite of cardiovascular mortality, non-fatal MI or stroke. This was in addition to an overall reduction in cardiovascular mortality (OR 0.82; 95% CI [0.76–0.88]; p<0.0001).

Renal failure and angioedema are contraindications to ACEI prescription. In such cases, ARBs can be an alternative therapy. ARBs differ in their mode of action from ACEIs by inhibiting the receptor binding of angiotensin II rather than inhibiting the conversion of angiotensin I to angiotensin II. The VALIANT (valsartan versus captopril) and ONTARGET (telmisartan versus ramipril) studies reported ARBs to have a similar efficacy as ACEIs in reducing mortality in patients with heart failure or left ventricular dysfunction after an episode of MI. The coadministration of ACEI and ARB is not advised due to detrimental effects on renal function and the increased risk of hyperkalaemia.

The India, and the Australia and New Zealand guidelines recommend cautious monitoring of blood pressure with special attention to postural hypotension during ACEI or ARB prescription.^{11,12} The India guidelines further specify that ACEIs should be started at a low dose and steadily ramped up to the target dose within 4 to 6 weeks.¹² In addition to this, renal function must be carefully monitored while determining the optimal dosage for the patient, followed by an annual check-up during long-term maintenance with an ACEI or ARB.¹² More recent evidence suggests the

use of angiotensin receptor neprilysin inhibitor (ARNI) in the post-MI protocol instead of ACEI.

Lipid-lowering Therapy with 3-hydroxy-3methylglutaryl-coenzyme A Reductase Inhibitors

Statement 6. Long-term administration of the maximum tolerable dose of a strong statin - 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor - is recommended in patients after an MI, irrespective of baseline LDL-C levels. Patients with statin intolerance may benefit from a reduced dose regimen of statin therapy.

Level of evidence: Strong Level of agreement: High

Statement 7. Ezetimibe and protein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) may be considered as the next line of lipid-lowering agents in cases of suboptimal LDL-C levels during statin therapy. Recent guidelines are aggressive with lipid lowering in very high-risk patients such as those who are post-MI.

Level of evidence: Strong Level of agreement: High

Statins inhibit the formation of atherosclerotic plaques by reducing the levels of LDL-C, stabilising the lipid core and reducing inflammation in arteries. 11 A meta-analysis of five RCTs comparing high- and low-intensity statin therapies concluded that the high-intensity therapy was more efficacious in risk reduction for cardiovascular death, non-fatal MI and ischaemic stroke.³⁸ High-dose atorvastatin 80 mg daily reduces ischaemic stroke and death in patients with cardiovascular disease and is recommended in all international guidelines. 10-15,39 The Japan and India guidelines recommend the use of high-intensity rosuvastatin 20-40 mg daily as well. 12,14 Evidence for the efficacy of other statins is currently lacking. Recent European Society of Cardiology guidelines recommend LDL <55 mg/dl for high-risk and <45 mg/dl for extreme-risk patients, such as those with recurrent events or polyvascular disease, while the Lipid Association of India guidelines suggest <50 and <35 mg/dl, respectively. To achieve this would be difficult and patients would require combination therapy and possible use of PCSK9i along with a high level of adherence to the therapy. The dosage of statins is variable and generally lower in certain Asia-Pacific countries due to low tolerance and high responsiveness.

Early administration of the maximum tolerable dose of statins, irrespective of baseline LDL-C levels is recommended by the Australia and New Zealand guideline. The guideline further states that a reduced dose regimen may be tolerated in patients with intolerance to high-intensity statin therapy. European, Australia and New Zealand, India, Japan and Taiwan guidelines recommend the use of ezetimibe 10 mg daily in patients who have no tolerance to statins or have sub-optimal levels of LDL-C despite statin treatment. Ezetimibe reduces intestinal cholesterol absorption. The IMPROVE-IT trial showed that the addition of ezetimibe to statin therapy achieved significantly lower levels of LDL-C and reduced the rates of MI, coronary revascularisation and stroke compared to statin therapy alone. Oronary revascularisation and stroke compared to statin therapy alone. The Australia and New Zealand guideline recommends lower-intensity statin therapy in case of side effects such as myositis.

PCSK9i are recommended as a secondary treatment for lowering lipids. 42 PCSK9i enhances the metabolism of LDL-C in the liver by inhibiting the

PCSK9 protein. The FOURIER and ODYSSEY OUTCOMES trials demonstrated that the addition of evolocumab or alirocumab to statin therapy in patients with a history of cardiovascular disease achieved a relative risk reduction of approximately 15% for the composite endpoint of cardiovascular death, MI, stroke and coronary revascularisation compared to a placebo administered with statin therapy. 43,44

The India and Japan guidelines further recommend considering fibrates for patients with hypertriglyceridaemia and low HDL-C level. 12,14 This recommendation is supported by a subgroup analysis of the FIELD study, which revealed that fenofibrate reduced cardiovascular events in patients with low HDL-C levels. 45 A systematic review and meta-regression analysis of RCTs studying the association between lowering triglyceride levels and the associated decrease in cardiovascular risks have shown similar findings. 46 In addition to the above therapies, the use of omega-3 fatty acids and ethyl icosapentate may be considered.

Lifestyle Modifications for the Secondary Prevention of MI

Statement 8. Smoking should be discontinued by patients with a history of MI.

Level of evidence: Strong Level of agreement: High

Statement 9. Regular aerobic physical activity to achieve a BMI of $20-25 \text{ kg/m}^2$ is recommended after an MI if there is no history of significant heart failure.

Level of evidence: Strong Level of agreement: High

Statement 10. A diet that supports blood pressure and BMI in the healthy range and includes the moderation of alcohol intake should be adopted.

Level of evidence: Moderate Level of agreement: High

Smoking cessation is important in the long-term management of patients with MI. Due to the addictive nature of the habit, professional counselling is often necessary. Pharmacotherapeutic aids such as electronic cigarettes and nicotine patches are advised by the expert committee for patients who are struggling to stop smoking and have not consented to professional counselling. Cessation of smoking should commence during hospitalisation when the patient is not allowed to smoke and patient adherence to a smoking-free lifestyle should be ensured during post-discharge visits. A meta-analysis of 20 observational studies revealed a 36% reduction in mortality among CAD patients (including those with MI) who stopped smoking. Further, the effectiveness of cigarette substitutes is indicated by two RCTs, which observed higher quitting rates or reduced smoking among patients using electronic nicotine cigarettes (compared to placebo). 47

Regular aerobic physical activity is an essential component of long-term secondary prevention after an MI. Patients new to exercising should seek exercise-based cardiac rehabilitation. According to data from a large-scale meta-analysis, exercise-based cardiac rehabilitation achieved a 22% reduction in cardiac mortality in patients with CAD. ⁴⁸ As part of long-term secondary prevention, aerobic exercise for 20–60 minutes a day at least five times a week, is strongly recommended. ^{12,14} Aerobic exercise should aim for a Borg's rating of perceived exertion of at least 11 and not exceeding

16.49 Counting steps per day may also be recommended to increase physical activity. A meta-analysis found a progressively decreasing risk of mortality among adults aged 60 years and older with an increasing number of steps per day up to 6,000-8,000 steps per day and among adults younger than 60 years up to 8,000–10,000 steps per day.⁵⁰ The expert committee also recommends resistance exercise as part of long-term management. As recommended by the American Heart Association, resistance training should be performed in a rhythmical manner at a moderate-to-slow controlled speed, without straining or holding of breath.⁵¹ The initial resistance should allow for 10 to 15 repetitions at a low level of resistance (e.g. <40% of the patient's one-repetition maximum). The initial programme should include one set of 10 to 15 repetitions per set of 8 to 10 exercises performed for 2 to 3 days per week. As the patient increases in strength, exercise dosage can be increased by gradually increasing the repetitions per set, which may later be supplemented by increasing the resistance, adding more sets per exercise and decreasing the rest period between sets or exercises.

ESC guidelines recommend a diet that includes high fibre (30–45 g/day), moderated salt (<5 g/day), low sugar, fruits and vegetables (200 g of each per day), polyunsaturated fatty acids and unsalted nuts (30 g daily) for patients with MI. 10 While the ESC guidelines allow for limited alcohol intake, the expert committee strongly discourages alcohol consumption and binge drinking in patients with left ventricular dysfunction. Further, the committee recommends that diet should be based on local habits, cultures, availability and affordability to produce meaningful results in a patient's cardiovascular health goals. The committee also recommends that the total calorie intake must be adjusted to achieve a BMI of 20-25 kg/m 2 and a waist circumference of 94 cm for men and 80 cm for women. In cases of obesity (BMI >25 kg/m 2), a reduction in body weight by 3% over a duration of 3 to 6 months is recommended.

Using lifestyle modifications to achieve a target systolic blood pressure (SBP) of <140 mmHg is desirable considering that hypertension is a risk factor in STEMI patients. For high-risk patients placed on intense pharmacotherapy to control blood pressure, a target SBP of <120 mmHg may be considered. 52,53

Cardiac Rehabilitation for the Secondary Prevention of MI

Statement 11. All patients should be offered a cardiac rehabilitation programme after MI, particularly after STEMI.

Level of evidence: Strong Level of agreement: High

Statement 12. Cardiac rehabilitation should be provided as a structured programme, which includes exercise training, lifestyle advice and psychological counselling aimed at returning the patient to normalcy.

Level of evidence: Strong Level of agreement: High

Statement 13. At the end of the cardiac rehabilitation programme, the patient must resume working, sports, recreation and sexual activity while self-monitoring biomedical indices and adherence to cardioprotective medication and lifestyle modifications.

Level of evidence: Moderate Level of agreement: High

As acute coronary syndrome patients spend only a short duration in hospital, they benefit from the evidence-based therapy provided by the outpatient cardiac rehabilitation programmes. In a systematic review of 63 studies in which patients were randomised to exercise-based cardiac rehabilitation or conventional care, a median follow-up of 12 months revealed a reduction in cardiovascular mortality (RR 0.74; CI 95% [0.64– 0.86]) and hospital readmissions (RR 0.82; CI 95% [0.70-0.96]) in the cardiac rehabilitation cohort. 48 Interestingly, the benefits observed were consistent across patient type (high- or low-risk), intervention type (comprehensive versus exercise-based rehabilitation) and the setting of rehabilitative care (at a centre, home or a combination of the two). Another study reported decreased platelet aggregation in patients who participated in a 3-month multidisciplinary cardiac rehabilitation (inclusive of diet, exercise and lifestyle modification), compared to those who were in a traditional care programme (single session dietary advice and group physiotherapy) under optimal DAPT.⁵⁴ A meta-analysis of 63 RCTs covering different cardiac rehabilitation formats, components and settings also observed a significant reduction in all-cause mortality over 24 months (RR 0.85; 95% CI [0.77-0.94]) for patients undergoing rehabilitative care. 55 Cardiac rehabilitation may have a pleiotropic effect in the recovery of cardiovascular disease patients. A cardiac rehabilitation programme of 8-24 weeks is recommended.

Remote access to cardiac rehabilitation services may also be effective. The CHOICE trial evaluated the differences in recovery between acute coronary syndrome patients who could access telephone support on mandatory cholesterol lowering and personalised risk modification measures with those who did not have access to centrally coordinated rehabilitative support.⁵⁶ After 12 months, patients with rehabilitative assistance fared better in terms of mean total cholesterol (156 mg/dl versus 183 mg/dl, p=0.001), systolic blood pressure (132 mmHg versus 144 mmHg, p=0.001), BMI (28.9 versus 31.2, p=0.025) and physical activity. A systematic review also found that home-based cardiac rehabilitation is safe with a low incidence of adverse events, hence it may be considered as a safe alternative form of cardiac rehabilitation.⁵⁷

The Australia and New Zealand guidelines specify that cardiac rehabilitation programmes should be flexible with a wide range of options and structures and that the patient may choose to attend any number of programmes in accordance to health risks. Advice on return to normalcy should be individualised according to a patient's left ventricular function, success in revascularisation, rhythm control during exercise and the stress levels dictated by their occupation. According to the expert committee's recommendation, return to sexual activity can be as early as 4 weeks after an MI if the patient's physical abilities are restored. The recommendation further suggests treating male erectile dysfunction with a phosphodiesterase type 5 (PDE5) inhibitor after 6 months of an MI incident.

It was seen that among patients who completed their cardiac rehabilitation programmes, the absolute risk of MI, stroke and cardiac death was 4.5% lower. When resources and infrastructure is limited, manuals, DVDs, phone calls and text message follow-ups should be implemented to help a patient with home-based personalised coaching. Bigger cities without infrastructural problems should aim to provide personalised and comprehensive cardiac rehabilitation services.

Discharge management should include clear documentation on medical and rehabilitative advice, including a copy of the patient's latest ECG. Patients should be provided with referrals for individualised preventive intervention according to personal preference and available resources.

The spectrum of services should include options for hospital-based, home-based, and local community-based settings for rehabilitative coaching.

Conclusion

The 13 statements in this review are the consensus recommendations of cardiology experts in the Asia-Pacific region, providing unified guidance on the secondary prevention practices for MI suited to the region. The consensus recommendations, which are feasible and effective for the practice of long-term care in STEMI and NSTEMI for the Asia-Pacific population, have taken into account local and international guidelines and opinions of regional experts, along with considerations for prevailing comorbidities, literacy rates, education levels and the tolerability, cost and availability of drugs in different countries in the Asia-Pacific region.

Management of Comorbidities

The management of comorbidities in patients with MI requires specific secondary prevention therapy. Recommendations specific to conditions such as diabetes, hypertension and chronic kidney disease are beyond the scope of this document. In patients with a history of heart failure or in those with heart failure that complicates MI, the committee recommends

existing guidelines, such as the ESC or the American Heart Association/ American College of Cardiology. Briefly, therapy may include diuretics, β-blockers, ACEI or ARB and a sodium-glucose transport protein 2 inhibitor. However, given Asia's highly variable socioeconomic status and public healthcare funding, therapy that is individualised to the patient is recommended. □

Clinical Perspective

- Secondary prevention of acute MI reduces cardiovascular mortality and hospital readmissions in recovered patients and aids a return to normalcy and improved quality of life.
- These consensus recommendations from the Asia-Pacific Cardiometabolic Consortium unify the approach to the long-term care of patients after MI, which can be applied across the Asia-Pacific region.
- Secondary prevention focused on strategies encompassing pharmacotherapy, lifestyle modifications, cardiac rehabilitation and discharge management for patients with a history of type 1 MI, specifically relating to atherosclerotic plaque rupture and thrombosis.

- Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circ Cardiovasc Qual Outcomes 2012;5:532–40. https://doi.org/10.1161/ CIRCOUTCOMES.111.964700; PMID: 22740013.
- Wood D, De Bacquer D, De Backer G, et al. A European Society of Cardiology survey of secondary prevention of coronary heart disease: principal results. Eur Heart J 1997;18:1569–82. https://doi.org/10.1093/oxfordjournals. eurheartj.a015136; PMID: 9347267.
- EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries: principal results from EUROASPIRE II Euro Heart Survey Programme. Eur Heart J 2001;22:554–72. https://doi.org/10.1053/euhj.2001.2610; PMID: 11259143.
- Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. Eur J Cardiovasc Prev Rehabil 2009;16:121–37. https://doi.org/10.1097/ HJR.0b013e3283294b1d; PMID: 19287307.
- Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: a European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2016;23:636– 48. https://doi.org/10.1177/2047487315569401; PMID: 25687109.
- Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med 2012;125:882

 –7.e1. https://doi. org/10.1016/j.amjmed.2011.12.013; PMID: 22748400.
- Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of myocardial infarction and StrokE (WHO-PREMISE). Bull World Health Organ 2005;83:820-9. https://doi.org//S0042-96862005001100011; PMID: 16302038.
- Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. Eur J Cardiovasc Prev Rehabil 2010;17:410–8. https://doi.org/10.1097/ HJR.0b013e32833442d2; PMID: 20300001.
- Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52. https://doi.org/10.1016/S0140-6736(04)17018-9; PMID: 15364185.
- Ibanez B, James S, Agewall S, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2018;39:119–77. https://doi.org/10.1093/eurheartj/ehx393; PMID: 28886621.
- Chew DP, Scott IA, Cullen L, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New

- Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. *Heart Lung Circ* 2016;25:895–951. https://doi.org/10.1016/j.hlc.2016.06.789; PMID: 2888662.
- Ministry of Health and Family Welfare, Government of India, New Delhi. Guidelines for the Management of Cardiovascular Diseases in India: part 1. http:// clinicalestablishments.gov.in/WriteReadData/149.pdf (accessed 9 June 2022).
- Li YH, Lee CH, Huang WC, et al. Focused update of the 2012 guidelines of the Taiwan society of cardiology for the management of ST-segment elevation myocardial infarction. Acta Cardiol Sin 2020;36:285

 –307. https://doi.org/10.6515/ ACS.202007_36(4).20200619A; PMID: 32675921.
- JCS Joint Working Group. Guidelines for secondary prevention of myocardial infarction (JCS 2011). Circ J 2012;77:231–48. https://doi.org/10.1253/circj.cj-66-0053; PMID: 23165785.
- National Institute for Health and Care Excellence. Acute coronary syndromes: NG185. London: NICE, 2020. https://www. nice.org.uk/guidance/ng185 (accessed 9 June 2022).
- Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6. https://doi.org/10.1016/j.jclinepi.2010.07.015. PMID: 21208779.
- Undas A, Brummel-Ziedins KE, Mann KG. Antithrombotic properties of aspirin and resistance to aspirin: Beyond strictly antiplatelet actions. *Blood* 2007;109:2285–92. https://doi.org/10.1182/blood-2006-01-010645; PMID: 17148593.
- Ledford DK, Lockey RF. Aspirin or nonsteroidal antiinflammatory drug-exacerbated chronic rhinosinusitis. J Allergy Clin Immunol Pract 2016;4:590–8. https://doi. org/10.1016/j.jaip.2016.04.011; PMID: 27393773.
- Mukherjee D, Topol EJ, Moliterno DJ, et al. Extracardiac vascular disease and effectiveness of sustained clopidogrel treatment. Heart 2006;92:49

 –51. https://doi.org/10.1136/ hrt.2005.064501; PMID: 8918275.
- Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): A randomised factorial trial. *Lancet* 2010;376:1233–43. Https://doi.org/10.1016/S0140-6736(10)61088-4; PMID: 20817281.
- James S, Axel A. Comparison of ticagrelor, the first reversible oral P2Y 12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient outcomes (PLATO) trial. Am Heart J 2009;157:599–605. https://doi.org/10.1016/j. ahj.2009.01.003; PMID: 19332184.
- Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl

- J Med 2015;372:1791–800. https://doi.org/10.1056/ NEJMoa1500857; PMID: 25773268.
- Costa F, Tijssen JG, Ariotti S, et al. Incremental value of the CRUSADE, ACUITY, and HAS-BLED risk scores for the prediction of hemorrhagic events after coronary stent implantation in patients undergoing long or short duration of dual antiplatelet therapy. J Am Heart Assoc 2015;4:e002524. https://doi.org/10.1161/JAHA.115.002524; PMID: 26643501.
- Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–15. https://doi.org/10.1056/ NEJMoa0706482; PMID: 17982182.
- Saito S, Isshiki T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome – the PRASFIT-ACS study. Circ J 2014;78:1684–92. https://doi. org/10.1253/circj.cj-13-1482; PMID: 24759796.
- Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9–19. https://doi.org/10.1056/NEJMoa1112277; PMID: 22077192.
- Freemantle N, Cleland J, Young P, et al. β blockade after myocardial infarction: systematic review and meta regression analysis. Br Med J 1999;318:1730–7. https://doi. org/10.1136/bmj.318.7200.1730; PMID: 10381708.
- McMurray J, Køber L, Robertson M, et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the carvedilol post-infarct survival control in left ventricular dysfunction (Capricorn) trial. J Am Coll Cardiol 2005;45:525–30. https://doi.org/10.1016/s0140-6736(00)04560-8; PMID: 11356434.
- Chen Z, Xie J. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1622–32. https://doi.org/10.1016/S0140-6736(05)67661-1; PMID: 16271643.
- Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 2004;292:2217–25. https://doi.org/10.1001/jama.292.18.2217; PMID: 15536108.
- Japanese Beta-Blockers and Calcium Antagonists
 Myocardial Infarction (JBCMI) Investigators. Comparison of
 the effects of beta blockers and calcium antagonists on
 cardiovascular events after acute myocardial infarction in
 Japanese subjects. Am J Cardiol 2004;93:969–73.
 https://doi.org/10.1016/j.amjcard.2004.01.006;
 PMID: 15081437.
- Dickstein K, Kjekshus J, OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial.

- Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002;360:752–60. https://doi.org/10.1016/s0140-6736(02)09895-1; PMID: 12241832.
- Dagenais GR, Pogue J, Fox K, et al. Angiotensin-convertingenzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006;368:581–8. https://doi. org/10.1016/S0140-6736(06)69201-5; PMID: 16905022.
- Herman LL, Padala SA, Ahmed I, et al. Angiotensin Converting Enzyme Inhibitors (ACEI). In: StatPearls. FL, US: StatPearls Publishing, 2021. https://www.ncbi.nlm.nih.gov/ books/NBK431051/.
- Brunner HR. Angiotensin II receptor blockers. In: Lip GYH, Hall JE, eds. Comprehensive Hypertension. 1st edn. Philidelphia, PA: Elsevier, 2007;1003–17. https://doi. org/10.1016/B978-0-323-03961-1.50084-2.
- Přeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893–906. https://doi.org/10.1056/ NEJMoa032292; PMID: 14610160.
- ONTARGET Investigators, Yusuf S, Teo KK, et al.Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–59. https://doi.org/10.1056/ NEJMoa0801317; PMID: 18378520.
- Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–81. https://doi. org/10.1016/S0140-6736(10)61350-5; PMID: 21067804.
- Amarenco P, Bogousslavsky J, Callahan A, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–59. https://doi.org/10.1056/ NEJMoa061894; PMID: 16899775.
- Giugliano RP, Cannon CP, Blazing MA, et al. Beneft of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus results from IMPROVE-IT (improved reduction of outcomes: vytorin effcacy international trial). Circulation 2018;137:1571–82. https://doi.org/10.1161/ CIRCULATIONAHA.117.030950; PMID: 29263150.
- 41. Tsujita K, Sugiyama S, Sumida H, et al. Impact of dual lipidlowering strategy with ezetimibe and atorvastatin on

- coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE–IVUS trial. *J Am Coll Cardiol* 2015;66:495–507. https://doi.org/10.1016/j.jacc.2015.05.065; PMID: 26227186.
- Loyd–Jones DM, Morris PB, Ballantyne CM, et al. Focused update of the 2016 ACC Expert Consensus decision pathway on the role of non–statin therapies for LDL–cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology task force on expert consensus decision pathways. J Am Coll Cardiol 2017;70:1785–1822. https://doi.org/10.1016/j.jacc.2017.07.745; PMID: 28886926.
 Murphy SA, Pedersen TR, Gaciong ZA, et al. Effect of the
- Murphy SA, Pedersen TR, Gaciong ZA, et al. Effect of the PCSK9 inhibitor evolocumab on total cardiovascular events in patients with cardiovascular disease: a prespecified analysis from the FOURIER trial. JAMA Cardiol 2019;4:613–9. https://doi.org/10.1001/jamacardio.2019.0886; PMID: 31116355.
- Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–2107 https://doi.org/10.1056/ NEJMoa1801174; PMID: 30403574.
- Hermans MP. Impact of fenofibrate on type 2 diabetes patients with features of the metabolic syndrome: subgroup analysis from FIELD. *Curr Cardiol Rev* 2010;6:112–8. https:// doi.org/10.2174/157340310791162686; PMID: 21532777.
- Marston NA, Giugliano RP, Im K, et al. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-regression analysis of randomized controlled trials. *Circulation* 2019;140:1308–17. https://doi.org/10.1161/CIRCULATIONAHA.119.041998; PMID: 31530008.
- Bond K, Nunes N. Electronic cigarettes for smoking cessation. Am Fam Phys 2016;93:492. https://doi. org/10.1002/14651858.CD010216.pub2; PMID: 26977834.
- Anderson L, Oldridge N, Thompson DR, et al. Exercisebased cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016;67:1–12. https://doi.org/10.1016/j. jacc.2015.10.044; PMID: 26764059.
- 49. Mytinger M, Nelson RK, Zuhl M. Exercise prescription

- guidelines for cardiovascular disease patients in the absence of a baseline stress test. *J Cardiovasc Dev Dis* 2020;7:15. https://doi.org/10.3390/jcdd7020015; PMID: 32349219.
- Paluch AE, Bajpai S, Bassett DR, et al. Daily steps and allcause mortality: a meta-analysis of 15 international cohorts. *Lancet Public Health* 2022;7:1–10. https://doi.org/10.1016/ S2468-2667(21)00302-9; PMID: 35247352.
- Williams MA, Haskell WI, Ades PA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. Circulation 2007;116:572–84. https://doi.org/10.1161/ CIRCULATIONAHA.107.185214; PMID: 17638929.
- SPRINT Research Group, Wright JT, Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood pressure control. N Engl J Med 2015;373:2103–16. https://doi. org/10.1056/NEJMoa1511939; PMID: 26551272.
- Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2009–20. https://doi.org/10.1056/NEJMoa1600175; PMID: 27041480.
- Tóth-Zsámboki E, Horváth Z, Hajtman L, et al. Cardiac rehabilitation programme as a non-pharmacological platelet inhibitory tool in acute coronary syndrome survivors. Eur J Prev Cardiol 2017;24:1148–56. https://doi. org/10.1177/2047487317704937; PMID: 28438028.
- Clark AM, Hartling L, Vandermeer B, McAlister FA. Metaanalysis: secondary prevention programs for patients with coronary artery disease. *Ann Intern Med* 2005;143:659–72. https://doi.org/10.7326/0003-4819-143-9-200511010-00010; PMID: 16263889.
- Neubeck L, Freedman SB, Briffa T, et al. Four-year followup of the choice of health options In prevention of cardiovascular events randomized controlled trial. Eur J Cardiovasc Prev Rehabil 2011;18:278–86. https://doi. org/10.1097/HJR.0b013e32833cca66; PMID: 20606594.
- Stefanakis M, Batalik L, Antoniou V, Pepera G. Safety of home-based cardiac rehabilitation: a systematic review. Heart Lung 2022;55:117–26. https://doi.org/10.1016/j. hrtlng.2022.04.016; PMID: 35533492.