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Medical Management of Stable Coronary Atherosclerosis

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Abstract Revascularisation strategies involving coronary artery bypass grafting or percutaneous interventions are the main treatments for stable coronary artery disease, particularly for patients with ongoing symptoms despite medical therapy and/or extensive ischaemia as demonstrated by either non-invasive or invasive means. Irrespective of whether revascularisation is being undertaken, all patients with stable coronary disease require optimal medical therapy in order to reduce the risk of subsequent adverse cardiac events, particularly acute myocardial infarction. The role of medical management has been very actively investigated and reported, particularly because of the global disease burden and the associated high morbidity and mortality. In this review, the current available medical management for the treatment of coronary atherosclerosis is described together with the role and prospects of the newer classes of drugs that are coming into use, and future perspectives in this field.

Keywords Coronary artery disease · Stable angina · Coronary atherosclerosis

Introduction

Coronary atherosclerosis is a multifactorial systemic disease that shows considerable variability in disease progression from individual to individual [1]. The treatment of coronary atherosclerosis has several major components, including identification of people at high risk of developing atherosclerosis, slowing disease progression and preventing coronary events, risk reduction in individuals who have already had a coronary event to offset further myocardial infarctions or cardiac death, and a reduction in symptom frequency and severity in those with established coronary artery disease (CAD).

There has been a continual debate on the issue of medical management in patients with stable CAD. Revascularisation with either coronary artery bypass grafting or percutaneous intervention (PCI) has a positive impact on symptoms in patients with ischaemic heart disease [2–4]; however, longer-term follow-up of several randomised controlled trials showed that these effects did not necessarily reflect an improvement in cardiovascular mortality [5, 6]. With a meta-analysis of 17 studies, Schömig et al. [7] showed that PCI might confer a prognostic advantage in terms of long-term survival. However, it must be considered that most of the studies included were historical and did not apply contemporary medical treatment, or newer advances in PCI, and this may have affected the results [8]. Controversy continues with results from recent clinical trials suggesting that patients with stable CAD are unlikely to receive prognostic benefits [9] unless the presence of significant ischaemia is demonstrated. However, it must be considered that the patients enrolled in the COURAGE trial were of relatively low risk, with low incidence of hard cardiac events during follow-up. Nearly 80 % had minimal or mild angina with mild to moderate ischaemia on the stress test [10]. Furthermore, in this trial one third of the patients, initially assigned to the optimal medical therapy group, crossed over to receive PCI. Thus, the beneficial effect of PCI may have been diluted by intention-to-treat analysis [11]. Patients whose revascularisation has clearly been shown to be beneficial in terms of prognosis are those with left main stem disease and three vessel disease [12, 13, 14•].

Advances in non-invasive imaging modalities have promise in combining functional and anatomical information that

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might improve the selection of patients who require revascularisation [15]. In fact, a nuclear imaging substudy of the COURAGE trial showed that showed that adding PCI to optimal medical therapy resulted in a greater reduction in ischaemia than medical therapy alone. In addition, residual ischaemia on follow-up was found to be proportional to the risk of death or myocardial infarction, and a 5 % or greater reduction in ischaemia was associated with a significant reduction in risk. However, it must be considered that on adjusted analysis, the authors failed to find an independent treatment effect on these results, considering also that moderate to severe ischaemia was present in only one third of cases [15].

Medical management is important in these individuals for both primary and secondary prevention. This field has been very active, reflecting the global disease burden and the associated high morbidity and mortality. We will review the current available medical management for the treatment of coronary atherosclerosis, which is fundamentally based on educational measures and a few long-established first-line treatment drugs [16–18] as well as at newer classes of drugs that have use in this field.

Tailoring a Correct Lifestyle

Promoting a healthy lifestyle is one of the main aims of primary and secondary prevention in patients with CAD. This has received enthusiasm and support from those in the medical and political communities. There is a large body of evidence supporting lifestyle changes as first-line therapy for reducing cardiovascular risk in both healthy individuals and patients with known CAD [19]. After an accurate anamnesis, the global risk of having a major cardiovascular event must be stratified and the treatment individualised, keeping in mind the differences in the patient's cultural and educational background.

Diet

Large epidemiological studies have looked at the importance of diet on cardiovascular outcome. Much focus has gone into looking at how individuals from the Mediterranean area suffer comparatively less CAD. The Mediterranean diet (with a high proportion of fruits and vegetables, legumes, olive oil, moderate amounts of red wine, and low consumption of red meats) has become the hallmark of healthy living, with numerous studies reporting a beneficial effect on cardiovascular disease burden [20]. A recent meta-analysis comprising 1.5 million people reported a reduced risk of all-cause and cardiovascular mortality in those adhering to a Mediterranean diet [relative risk 0.91 (0.89-0.94); relative risk 0.91 (0.87-0.95); $P<0.0001$ for both], which translated to a 9 % reduction for both outcomes [20].

Different single nutrients have also been analysed in isolation to elucidate their role in atherosclerotic disease. Lycopene, an open-chain unsaturated carotenoid found in tomatoes, has been reported to attenuate atherogenesis via numerous mechanisms [21]. Quercetin, a flavonoid found in numerous fruits and vegetables (particularly onions), has also been shown to reduce atherosclerosis via its antioxidative properties [22]. In vitro studies have shown that quercetin, via blockade of the extracellular-signal-regulated kinase pathway, inhibits the expression of matrix metalloproteinase-1, an enzyme implicated in plaque destabilisation [23]. Anthocyanins, found in the outer pigmented layer of black rice, have been shown to inhibit the formation of atherosclerotic plaques in animal models [24]. These beneficial effects of dietary substances can be counteracted by processed foods. An increase in the intake of acrylamide, found in processed potato chips, was shown to increase the number of reactive oxygen radicals and inflammatory markers [25], which could be indicative of adverse prognosis in atherogenesis.

The interplay between diet and atherogenesis is multifaceted and complex. Numerous dietary elements have come under scrutiny because of their potential for stabilising plaques, although definitive conclusions are difficult to derive owing to the multitude of interactions. Overall, results support the principle that a healthy diet will confer benefits in CAD, and therefore a healthy diet should be encouraged regardless of age or morbidities.

Smoking

With an estimated one billion smokers worldwide, tobacco use has remained one of the main modifiable risk factors for the development of cardiovascular disease [26]. Cigarette smoke contains thousands of chemicals, of which only relatively few have been isolated and singled out as atherogenic, but the overwhelming evidence is one of poor prognosis for those who cannot stop smoking. National campaigns highlighting the hazards appear to have had limited success. Smoking is associated with a significantly increased likelihood of myocardial infarctions and with a dose-dependent relationship with the duration of smoking and the number of cigarettes smoked [27].

Smoking has been shown to have a number of effects on the cardiovascular system. Accelerated coronary artery calcification secondary to prolonged tobacco use has been proposed as a possible mechanism [28]. Smoking contributes to endothelial dysfunction by significantly inhibiting vasodilatation, most likely by interacting with intracellular protease activity [29]. Smoking increases the concentrations of intravascular free radicals, which interfere with lipid biosynthesis as a result of oxidative damage [30]. Its effect on thrombus formation is well known,

with smoke chemicals interfering and inhibiting tissue plasminogen activator, culminating in reduced fibrinolysis [31].

There is a vast body of evidence supporting the positive effects of smoking cessation on cardiovascular morbidity and mortality [32], and therefore such cessation programmes must continue to be encouraged and supported.

Exercise

Sedentary lifestyles predispose individuals to an increased risk of cardiovascular disease [33]. Regular physical activity can confer a multitude of benefits on the cardiovascular system, including endothelial adaptations that culminate in cardioprotection owing to a reduction in dysfunction, augmentation of the levels of circulating factors such as insulin and leptin, and an increase in circulating angiogenic cells that maintain and repair arteries [34]. The levels of inflammatory mediators and haemostatic biomarkers and blood pressure are all reduced as a result of moderate physical activity. Moreover, there is a reduction in LDL and triglyceride levels, and a rise in HDL levels secondary to exercise [35]. The burden of obesity continues to rise globally, and this is particularly high in younger people [36]. That has been shown to translate into early atherosclerosis in overweight children [37]. It is likely that if this trend continues, there will be a growing number of individuals presenting earlier with cardiovascular complications. Improved education could counteract this trend, but the impact has been very limited thus far. More needs to be done to encourage lifelong participation in physical activities. Even moderate aerobic exercise for 3 h per week has been shown to favourably modify the lipid profile [38]. Maintenance of physical activity is also a beneficial component of secondary prevention. Cardiac rehabilitation incorporating exercise programmes has been shown to reduce the risk of mortality and cardiovascular events after myocardial infarction [39]. The benefits of exercise are positively correlated with the type and duration of physical activity, and physical activity should be encouraged and adopted in both primary and secondary prevention, since inactivity remains a major modifiable risk factor for cardiovascular disease.

However, despite an extensive body of evidence favouring the prognostic beneficial effect of exercise, in recent years studies have been published showing a prognostic paradox in patients with coronary disease as underweight patients demonstrate a relatively high mortality and the lowest mortality is evident in overweight and obese patients [40]. The reasons are still unclear; however, the paradox may be related to the lack of discriminatory power of the body mass index to differentiate between body fat and lean mass [41] or to some statistical biases not clearly shown so far [42].

Tailoring the Right Drug to Those Who May Benefit

Statins

Statins have been accepted as the mainstay of lipid management for nearly 20 years. Reductions in LDL and triglyceride levels, coupled with increases in HDL cholesterol levels, are thought to confer benefits in cardiovascular disease [43]. The mechanism of action of statins has attracted much research interest, owing not only to the clinically proven benefits, but additionally to the safety and efficacy of the drug. Statins are acknowledged as the best drug in reducing LDL levels, but their beneficial pleiotropic effects may extend to modulation of inflammation, thrombogenicity, endothelial function [44, 45] and plaque stability or even regression [46], increasing the number of people who may benefit from them. In fact, the JUPITER trial looked at the role of the addition of rosuvastatin in apparently healthy subjects with no hyperlipidemia but high levels of high-sensitivity C-reactive protein. Compared with controls, individuals receiving 20 mg rosuvastatin had a lower incidence of adverse cardiovascular outcome, as well as a reduction in the inflammatory response [47].

Several studies have corroborated the findings that statin therapy yields better overall mortality outcomes. Large randomised controlled trials have shown that statin therapy significantly reduces mortality in patients with known cardiovascular disease [48], and confers benefit in those with other risk factors for the development of CAD [49, 50]. Those benefits are preserved in high-risk individuals older than 70 years. In the PROSPER (pravastatin in elderly individuals at risk of vascular disease) study, mortality from coronary disease fell by 24 % (p=0.043) in the group treated with 40 mg pravastatin per day after a follow-up period of 3 years [51].

The extent of reduction of LDL cholesterol levels differs according to the dose and type of statin used [52], but greater benefits regarding cardiovascular outcome appear to be dependent on overall reduction of LDL levels: when a more intensive treatment regimen is instituted, a highly significant further reduction in the risk of major cardiovascular events is observed [53••]. Higher doses of statins might be associated with a higher risk of developing diabetes [54••]. Finally, although male gender seems to confer a more apparent beneficial effect of statins lowering lipid levels in primary prevention, the gender effect remains neutral in secondary prevention of CAD [55•].

Ezetimibe and Other Drugs

Ezetimibe reduces absorption and processing of cholesterol by inhibiting the Niemann–Pick C1-like 1 protein [56]. In clinical practice, use of ezetimibe is generally reserved for

patients who are intolerant to statins. The ENHANCE trial looked at combination treatment of simvastatin and ezetimibe versus simvastatin alone in patients with familial hypercholesterolemia, and showed that the rate of progression of atherosclerosis in carotid intima–media thickness (CIMT) was not statistically different after 24 months of follow-up [57]. The results of the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6—HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER6-HALTS) trial showed that a reduction in CIMT could be obtained by adding niacin, but not ezetimibe, to current statin treatment [58]. Although it may be questionable if a reduction in CIMT reflects a reduction in the risk of cardiovascular events [59•], some patients, particularly those at high risk, may still benefit from the addition of ezetimibe as adjuvant therapy in lowering cholesterol levels and also the risk of adverse atherosclerotic events [60].

Niacin (nicotinic acid) has been used for the management of dyslipidaemia owing to its actions on the complex intracellular mechanisms governing triglyceride synthesis and lipolysis [61]. The beneficial effects of niacin on cardiovascular disease are attributed to its ability to reduce atherogenic triglyceride and LDL levels, with values quoted at 50 % and 25 %, respectively [62]. Moreover, niacin was noted to increase HDL cholesterol levels and to cause significant regression of coronary arterial atherosclerosis following long-term combination therapy with niacin and simvastatin [63]. In high-risk groups already receiving statin therapy, the addition of niacin resulted in significant reductions in carotid wall area as assessed by magnetic resonance imaging after 1 year [64•]. However, it seems that the use of niacin as an adjunct to conventional lipid-lowering therapy does not add any incremental clinical benefit if patients have reached their therapeutic target [65].

Omega-3 polyunsaturated fatty acids (PUFAs) can be found in oily fish and fish oils. It is well known that fish consumption is inversely associated with fatal coronary heart disease. A high intake of fish may reflect a healthier lifestyle [66], but some of the positive effects on long-term outcome could be attributable to omega-3 PUFAs and to their ability to lower plasma levels of triglycerides, decrease platelet aggregation, and reduce inflammation [67•]. They might have favourable effects on the cholesterol profile, decreasing VLDL and increasing HDL levels, but a rise in LDL levels has been also reported, even in high-risk populations. So far, the long-term benefits of high-dose fish oil supplements for the general population or for individuals with CAD remain uncertain [66, 67•].

Fibrates are another potential lipid-modifying drug that may be used in conjunction with statins in treatment-resistant patients. They bind to the intracellular peroxisome-proliferator-activated receptors and activate transcription factors. The downstream effects include increased lipolysis, induction of fatty acid uptake in hepatic cells, reduced triglyceride production, increased breakdown of LDL and increased HDL production [68]. Larger multicentre trial data have, however, been discouraging. The FIELD study, which assessed the effects of fibrates in diabetic patients, did not show a reduction in the incidence of coronary events after long-term follow-up [69]. Moreover, combination therapy with simvastatin did not result in a reduction in the incidence of coronary events in the ACCORD study [70•].

Antiplatelets

Antiplatelet agents are recognised as the gold standard for the treatment of atherothrombosis, and their potential benefits are thought to be conferred by a reduction in platelet aggregation, reduction in overall thrombus burden and formation, and reduction in vascular inflammation. More than 25 years ago, the ISIS-2 trial demonstrated that a low dose of aspirin given for 5 weeks after an acute myocardial infarction was associated with a better cardiovascular outcome [71]. Since then, a considerable amount of research data has been produced in this field. However, several meta-analyses have shown that, in high-risk patients, use of antiplatelet agents for primary prevention may result in more harm than benefit [72]. The Swedish Angina Pectoris Aspirin Trial (SAPAT) was the first prospective study of aspirin in stable angina. The addition of use of aspirin to a use of a beta-blocker (sotalol) resulted in a 34 % reduction for a combined primary outcome of myocardial infarction and sudden death during a 4-year follow-up [73]. Clopidogrel, as an alternative to aspirin in preventing further ischaemic events, has been shown to be as effective as aspirin, with the same safety profile [74]. The newer agents prasugrel and ticagrelor have a more reliable and potent antiplatelet effect than clopidogel and have demonstrated improved outcomes in patients with acute coronary syndromes (REF TRITON-TIMI 38 and PLATO). However, their role in the treatment of stable CAD has not yet been defined, despite some studies that claim a potential beneficial role as compared with aspirin or clopidogrel [75, 76]. To confer long-term prognostic advantages, questions about the optimal duration of treatment, and combination of therapies beneficial for different groups of patients, still need to be addressed and defined [77].

Drugs That Slow Heart Rate

Beta-blockers may have a role in slowing the progression of atherosclerosis. A pooled analysis conducted from four intravascular ultrasonography trials with a total of 1,515 patients showed that the volume of atheroma decreased at follow-up in patients who received beta-blockers, whereas there were no significant changes in patients who did not receive beta-blockers [78]. Beta-blockers have been shown to reduce mortality after a myocardial infarction [79] and

may be a valid treatment for patients with stable angina, but there have been no placebo-controlled trials to date to confirm this. Furthermore, recently published data from the REACH registry questioned those benefits in the current era, where more resources are available [80]. Beta-blockers and calcium antagonists both appear to be well tolerated, with no difference in their overall effects on mortality, cardiovascular end points and measures of quality of life in patients with CAD. Those measures of outcome were studied in the Angina Prognosis Study in Stockholm (APSIS) comparing metoprolol and verapamil in a cohort of 809 patients with stable angina, and similar results were observed for each drug given [81]. The Total Ischaemic Burden European Trial (TIBET) enrolled 682 patients with a diagnosis of chronic stable angina randomised to receive atenolol, nifedipine or their combination. This study showed no advantages in taking one drug over the other [82]. A meta-analysis of 90 studies compared the effects of beta-blockers and calcium antagonists, but the outcome results were driven by previously cited studies, which accounted for most of the events recorded. However, compared with the use of calcium antagonists, the use of beta-blockers was associated with fewer episodes of angina per week [83].

Ivabradine is a pure bradycardic agent that inhibits the I_f channel, a pacemaker current in the sinoatrial node and, according to the European Society of Cardiology guidelines, its use is indicated in patients with angina who do not tolerate beta-blockers. Its antianginal and anti-ischaemic effects have been well proven [84, 85]. The recently published ADDITIONS: Practical Daily Efficacy and Safety of Procoralan in Combination with Betablockers study, with more than 2,300 patients, showed that the addition of use of ivabradine to use of beta-blockers for 4 months not only decreased the number of anginal episodes, but was also associated with an improvement in the quality of life of patients with stable angina pectoris [86]. Furthermore, in a selected population, ivabradine may add significant prognostic advantages. In a subanalysis of the BEAUTIFUL (morbidity–mortality evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) study [87] conducted in patients with limiting angina and left ventricular systolic dysfunction, ivabradine significantly lowered the incidence of major cardiovascular events, particularly when the heart rate was higher than 70 beats per minute: in those patients, a 73 % ivabradine-related reduction in hospitalisation for fatal and non-fatal myocardial infarction and a 59 % reduction in coronary revascularisation was observed. Results from the SIGNIFY trial are awaited: it is currently ongoing and will address the effect of ivabradine on cardiovascular events in patients with angina and no clinical diagnosis of heart failure [88].

Nitrates and Newer Antianginal Drugs

Nitrates are venous dilatators that decrease the left ventricular filling pressures, thereby facilitating the diastolic coronary flow. Their use is mainly limited to symptomatic relief, and the development of tolerance with time can be attenuated with their intermittent use [89, 90]. Use of nitrates in patients with stable CAD does not seem to give major prognostic advantages during a short or medium period of time after an acute myocardial infarction [91, 92].

Nicorandil activates the potassium channel and increases nitric oxide levels [93]. It has been shown to be as safe and as effective in symptom relief as nitrates [94], but it might also offer beneficial prognostic advantages for patients with stable CAD. The Impact of Nicorandil in Angina (IONA) study included 5,126 patients with angina, and the results suggested that nicorandil therapy added on top of conventional therapy might reduce the risk of ischaemic cardiovascular events when compared with placebo [95]. Furthermore, the effects of nicorandil on outcome events were investigated in a prospective observational study of a large cohort of patients who had angiographic evidence of CAD (Japanese Coronary Artery Disease Study). The likelihood of deaths from all causes and fatal myocardial infarction were reduced by 35 % in patients treated with nicorandil [96].

Trimetazidine is a drug that improves myocardial utilisation of energy by its effect at numerous stages of the metabolic pathway, resulting in an effective anti-ischaemic treatment when added to standard treatment. The Trimetazidine in Angina Combination Therapy (TACT) study enrolled 177 patients with angina. A combination of trimetazidine and beta-blockers or nitrates resulted in better exercise functional capacity as well as lower frequencies of episodes of angina symptoms when compared with placebo [97]. Similar results were found in the TRIMPOLII study, which enrolled 426 postrevascularisation patients with effort angina. Compared with placebo, the use of trimetazidine increased ischaemic threshold, whilst also decreasing the number of angina attacks and nitrate consumption per week [98].

Ranolazine is a promising and attractive metabolic compound, and may have numerous other clinical applications in addition to symptomatic control of angina. In myocardial ischaemia, the late inward current of sodium becomes persistent and vast, causing a consequent rise in calcium concentration via the sodium–calcium exchanger. This mechanism causes the heart to function excessively, resulting in increased myocardial stiffness and vascular compression. Ranolazine, a selective inhibitor of the late sodium channel, decreases the late inward sodium current and consequently the intracellular calcium accumulation,

improving the diastolic phase of the heart cycle [99, 100]. Results from several randomised controlled trials indicate that ranolazine effectively reduces the frequency of episodes of angina and prolongs the time of exercise [101, 102] in patients with stable CAD.

The overall effects of these two metabolic drugs on the prognosis of patients with stable angina are still to be determined.

Antihypertensive Drugs

Management of arterial hypertension remains essential in stable CAD. The American Heart Association's scientific statement on the treatment of hypertension in the prevention and management of ischaemic heart disease clearly defines the blood pressure targets according to the cardiovascular risk profile [103].

Beyond the well-shown effect of blood pressure reduction, blockade of the renin–angiotensin system is the first choice for its additional antiatherosclerotic effect via the inhibition of the deleterious effects of angiotensin II, reduction of plasma LDL oxidation and overall attenuation of disease progression [104].

Many large randomised trials using ACE inhibitors or angiotensin receptor blockers have shown that use of these lowers the cardiovascular risk [105, 106] in patients with relatively normal baseline blood pressures. It is possible that this reflects a contribution of anti-inflammatory and antiatherosclerotic properties of these classes of drugs more than a pure blood pressure reduction. Those effects might not be evident when patients are at lower risk of cardiovascular events, such as those enrolled in the Prevention of Events with Angiotensin-Converting Enzyme Inhibitor Therapy (PEACE) trial [107]: this study did not show any benefit of trandolapril versus placebo in patients who had stable angina and preserved systolic function. However, most of the patients enrolled in this trial were treated intensively (70 % of the patients in the PEACE trial received cholesterol-lowering tablets, as compared with 29 % in the HOPE trial and 56 % in the EUROPA trial) and those in poor health were excluded. However, ACE inhibition appears to have more prognostic beneficial effect compared with the angiotensin receptor blockers [108].

If further blood pressure lowering is needed, a thiazide diuretic or a dihydropyridinic calcium channel blocker, or both, still remains a safe choice [103, 109].

Beyond all the evidence in favour of medical therapy, prescription of such therapy is often suboptimal, as recently shown by a large registry of patients with stable coronary disease undergoing PCI [110•]. There are several reasons for this, including lack of compliance, especially over the longer term, where education of the patients to remain on the full therapy is crucial [111].

Future Directions

There has been a shift of focus to the role of inflammation in atherosclerotic plaque progression and/or destabilisation, and these ongoing clinical trials may lead to the discovery of new agents in the fight against cardiovascular disease. Darapladib is an inhibitor of the enzyme lipoprotein-associated phospholipase A2, which is responsible for the local regulation of lipid metabolism and inflammation. Two large phase III trials [the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial (STABILITY) and the Stabilization of Plaques Using Darapladib–Thrombolysis in Myocardial Infarction 52 Trial (SOLID-TIMI 52)] are studying the impact of this drug on major cardiovascular outcomes for patients with acute or chronic CAD [112, 113]. The clinical impact of another well-known anti-inflammatory drug, methotrexate, will be studied in the Cardiovascular Inflammation Reduction Trial (CIRT) in people with type 2 diabetes or metabolic syndrome who have had a myocardial infarction [114]. Canakinumab binds interleukin-1β, and the ongoing CANTOS trial is evaluating its effects on cardiovascular outcome and plaque composition in patients with known CAD [115]. The Targeting Inflammation Using Salsalate in Cardiovascular Disease study [116] is a randomised clinical trial that is evaluating the effects of another anti-inflammatory drug, salsalate, on coronary artery plaque volume in patients with cardiovascular disease.

Conclusions

Many different options, including lifestyle changes or therapies, have been shown to be effective against atherosclerotic progression in the general population and in patients with established ischaemic heart disease. Other aspects of atherosclerosis, such as inflammation, have been increasingly acknowledged during the past few years and might offer new targets of treatment soon. Current evidence suggests that there is no 'magic bullet' for the treatment of stable coronary atherosclerosis, but that effective management depends on a personalised approach combining medical regimens unique to the individual, in addition to a strong emphasis on a healthy lifestyle.

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