REVIEW

Cardiovascular prevention: Lifestyle and statins – competitors or companions?

L H Opie, MD, DSc, FCP (SA, Hon); **A J Dalby**, FCP (SA), FACC, FESC

Prof. Lionel Opie is Director Emeritus at the Hatter Institute for Cardiovascular Research in Africa, Faculty of Health Sciences, University of Cape Town, South Africa. Dr Anthony Dalby is a cardiologist in private practice at the Milpark Hospital, Johannesburg, South Africa.

Corresponding author: *L H Opie (lionel.opie@uct.ac.za)*

Favourable lifestyles promote cardiovascular protection. Exercise can induce beneficial changes in the genome that decrease low-density lipoprotein cholesterol (LDL-C) and increase anti-inflammatory markers. The Mediterranean dietary pattern, fortified by nuts, while not reducing weight, reduces mortality. Lifestyle changes combined with statin therapy provide potent protection against coronary heart disease, especially when used for secondary prevention after cardiovascular events. Decisions regarding the initiation of statin therapy for primary prevention are more difficult, requiring consideration of both the LDL-C level and the degree of cardiovascular risk for dyslipidaemic patients. Combining intensive exercise and statin therapy substantially reduces the mortality risk, and thus is potentially the ideal risk-reducing combination.

S Afr Med J 2014;104(3):168-173. DOI:10.7196/SAMJ.7942

This review evaluates the beneficial effects of lifestyle (including exercise and diet) and of statins by considering the strength of data for each individually and their combination. The focus is on those studies with 'hard' endpoints, namely cardiovascular events and/or mortality. This approach is similar to that which formed the basis of the 2013 guidelines of the American College of Cardiology (ACC) and American Heart Association (AHA) which evaluate the relationship between statin therapy and the reduction in hard endpoints.[1]

The major components of the beneficial lifestyle were first defined in two long-term studies on American health professionals – the Women's and Men's Health Studies (Fig. 1.)[2-4] Those lifestyle factors were non-smoking (36% relative risk reduction in total deaths), exercise for ≥30 min daily (22%), ideal body weight (18%), an ideal diet (16%) and modest alcohol intake (9%). Mortality rose sharply as the number of risk factors increased. Lifestyle risk factors were cigarette smoking (ever), lack of physical activity (<30 min/day moderate- to vigorous-intensity activity), low diet quality (lowest three-fifths of healthy diet score), overweight (body mass index ≥25 kg/m^2) and an alcohol intake of 0 or ≥15 g/day. Diet and exercise are part of an overall pattern of healthy living applicable not only to privileged professionals but to all racial groups including the less affluent and those living in large cities.[5]

Lifestyle: Exercise and dietary patterns

Exercise training: What can it do?

While there are many benefits of regular exercise such as better subjective health and better sleep, a major benefit is countering cardiovascular disease (CVD). Thus, regular exercise can lower blood pressure (BP) in hypertensives by 11/8 mmHg.[6] This requires 30 - 60 min of exercise 3 - 5 times per week at a moderate walking pace, which is as good as an intensive walking pace. Greater degrees of ambulatory activity provide an incremental benefit to those at high cardiovascular risk.[7] In patients with chronic heart failure, exercise training lessens mortality.[8] Experimentally, exercise training gives protection after experimental reinfarction.[9]

Thorough cardiovascular assessment

The ability to undertake high levels of exercise such as marathon running, does not ensure protection from myocardial infarction or death.[10] Thus, the intention to

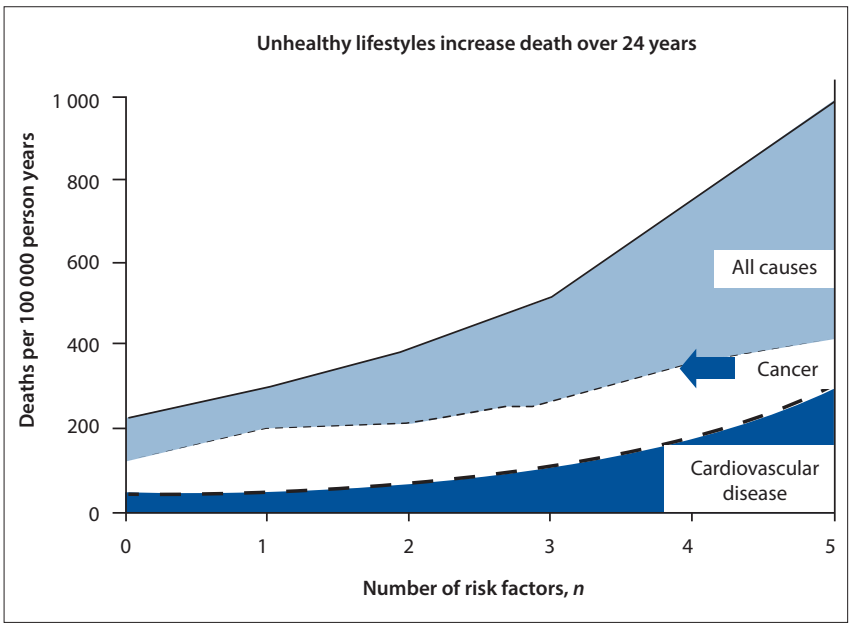

Fig. 1. All-cause, cardiovascular and cancer mortality over 24 years in the Women's Health Study in relation to the number of risk factors present. Figure from Opie,[46] modified from data from Dam et al.[4]

undertake intensive exercise training requires a medical history, blood lipids and an exercise electrocardiogram before starting.

Exercise reduces low-density lipoprotein cholesterol (LDL-C)

Taking into account data from 11 major outcome studies, intense exercise would reduce the 10-year risk of a coronary heart disease (CHD) event from 5% to just under 4%, while with statins, the greater LDL-C reduction would reduce the risk from 5% to about half that (2.5%).[11] The apparently unexplained aspect of these data is exactly how exercise reduces LDL-C. In part, the effect may be the result of other lifestyle changes often associated with intense exercise such as a better diet and weight loss, but the unexpected change specific to exercise is, surprisingly, that in the genome.

Exercising the genome

The explanation of why vigorous exercise promotes health independently of other lifestyle changes comes from studies on identical same-sex twins who were either persistently physically active or inactive throughout their lives.[12] Gene expression in adipose tissue and in skeletal muscle was quantified by nuclear magnetic resonance spectroscopy to yield the metabolome. The altered gene expression in the muscle of the active twins was associated with increased fatty acid oxidation, while in adipose tissue, fatty acid storage was decreased (Fig. 2).

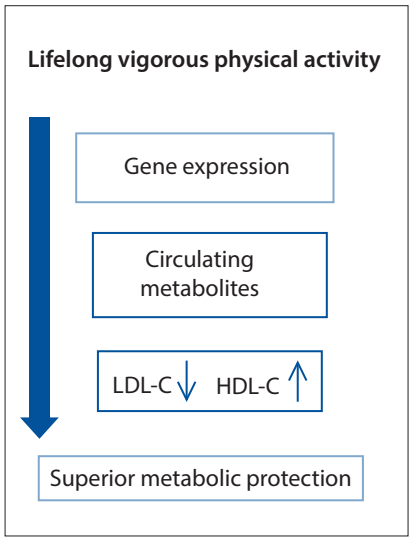

Fig. 2. Effects of persistent lifelong physical activity on the genomic pattern, which results in beneficial changes in circulating metabolites. For detailed proposals refer to Kujala et al.[12] *Note, the beneficially decreased serum low-density lipoprotein cholesterol (LDL-C) and increased high-density lipoprotein cholesterol (HDL-C) levels.*

The major metabolic changes between active and inactive twins were that blood glucose was lower in the physically active twins ($p<0.001$), serum fatty acid composition shifted towards a less saturated profile, and lipoprotein subclasses towards lower very-low-density lipoprotein (V-LDL) ($p<0.001$), all of which are associated with lower risks of CHD. Taken together, these data prove that intense lifelong exercise can on its own induce beneficial changes in the expression of the genome unassociated with any other lifestyle change.

Food, diet and health

Food patterns and long-term weight loss

There are strong links between food patterns (as opposed to calorie-restricted diets) and cardiovascular health. In the American health professionals studies, with participants eating their normal pattern of food, and not on any diet, weight gain was associated with eating potato chips, potatoes, meats, butter, refined grains, sweets and desserts.[13] Small amounts of weight loss were associated with regular eating of vegetables, nuts, whole grains, fruit and yoghurt. Among weight-gainers, the worst offenders were sugar-sweetened beverages and 100% fruit juices. These relatively small changes in weight play a modest role in cardiovascular prevention.

Diets: low-fat, high-fat, low-carbohydrate and others

It is important to distinguish between 'diet' in the sense of patterns of eating food and the usual weight-reducing diets; it is chiefly the former that will now be evaluated. The ideal trial should have sufficient statistical power to demonstrate which dietary pattern produces a clear endpoint difference in CVD and/or mortality. The 2-year Israeli study fell short of this ideal even though adherence rates were excellent.[14] Subjects were allocated to one of three diets: a low-fat diet, the Mediterranean diet, or a low-carbohydrate diet, which has much in common with the New Atkins diet.[14] Weight loss over 2 years was greatest on the low-carbohydrate diet (4.7 kg from an initial 90 kg), while LDL-C fell most on the Mediterranean diet. This study illustrates that even 2 years of strict dietary adherence is insufficient to impact on cardiovascular endpoints, a recurring problem when evaluating diets.

The very-low-carbohydrate, high-protein, high-fat Banting diet is closely related to the Atkins diet.[15] It allows more attractive foods and has good data to show weight loss and decreased insulin sensitivity, but at the cost of increasing LDL-C.[16] However, there are no reports on major outcomes such as CVD and/or mortality. Indeed, as Noakes[17] points out, large, well-designed outcome trials are urgently needed to test this hypothesis. In contrast, the Japanese diet is high in carbohydrate, containing much rice and little fat, yet the Japanese live longer than others. Perhaps the accompanying fish is protective, or maybe the secret lies in eating slowly.

Another new diet with beneficial metabolic changes, which include a decreased LDL-C, is the New Nordic Diet, which is high in fruit, vegetables, whole grains and fish.[18] It has the merit of reducing both body weight and BP in centrally obese individuals but so far lacks data on CVD reduction.[18]

Though a wide variety of diets is proposed, most lack comparative data, do not consider what each diet can achieve in terms of weight loss (if needed), blood lipid patterns and projected cardiovascular benefits, while simultaneously ensuring good compliance. Dietary adherence is enhanced by enthusiastic input, attractive presentation and personal contact.[15]

Dietary patterns that reduce mortality

The Mediterranean diet reduces mortality by 25%, CHD deaths by 33%, and cancer by 24%.[19] Its beneficial components are a high intake of vegetables, legumes, fruits and nuts, cereal, fish and monounsaturated fats, with small amounts of meat, poultry and high-fat dairy products.

Two studies link specific components of the Mediterranean dietary pattern to decreased mortality. In the first, in persons at high cardiovascular risk, the Mediterranean diet was supplemented with either extra-virgin olive oil or nuts. This reduced the incidence of major cardiovascular events and deaths.[20] Both nuts and olive oil possess cardioprotective qualities, albeit with differing mechanisms.[21] The second study narrowed down the specific beneficial component to nuts[22] as part of a lifestyle that increased physical activity, and fruit or vegetables, and avoided smoking and dietary red meat. While the overall data favour the Mediterranean dietary pattern, it seems simpler to add more nuts to the diet especially if that specifically decreases mortality.

Diet plus exercise as part of a beneficial lifestyle

This combination accounted for 30% of the overall lifestyle benefits in the American health professionals studies (Table 1). Diet, exercise and not smoking would account for 58% of the benefit. Experimentally, the damage caused by a very high-fat diet in rodents was reduced by exercise, the

Table 1. The lifestyle beneficial 'big five'*,†

Lifestyle big five	Protection from death, % (frequency)‡	Mechanism proposed
Non-smoking	28 (35)	Protects arteries
Exercise (≥30 min/day)	17 (22)	Slows the heart, lowers BP
Ideal weight	14 (18)	Avoids the toxic substances released from fat cells
Ideal diet	13 (16)	High unsaturated fatty acids, high fruit and vegetables, less red meat
Modest alcohol	7 (9)	Anti-stress, alcohol improves blood cholesterol patterns
All five	79 (100)	

BP = blood pressure.
*Note that successful coping with stress is not listed and may be estimated at 20 - 25% of the total lifestyle beneficial pattern.
†Table constructed from American health professionals studies.[2,4]
‡Deaths from all causes, including heart, stroke and cancer. Values in brackets indicate the frequency of the five lifestyle factors listed.

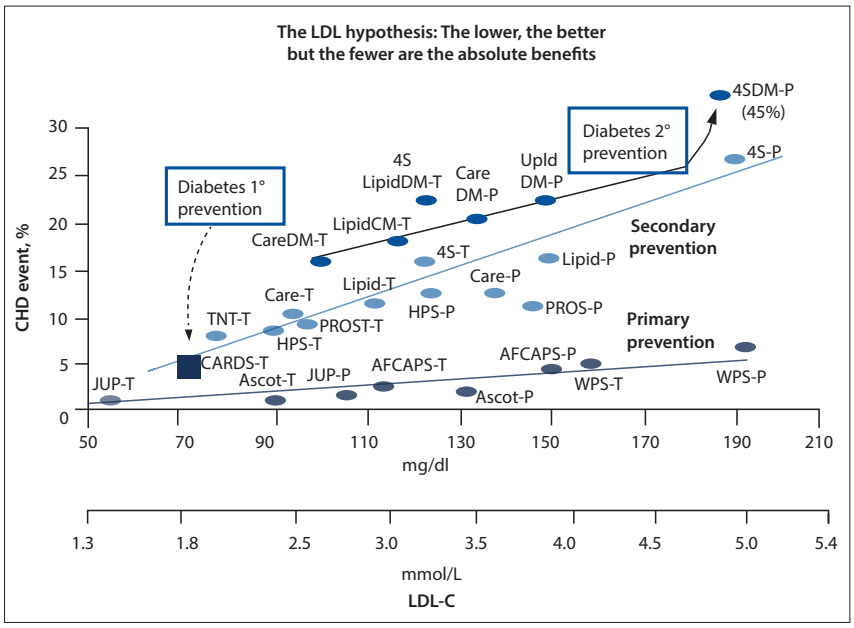

Fig. 3. Relationship between low-density lipoprotein cholesterol (LDL-C) levels and coronary heart disease (CHD) events in major trials for primary and secondary prevention. The lower the LDL-C, the fewer the 10-year events. Note the far greater effects with secondary than with primary prevention and especially marked effects in diabetics. For original figure and details of trials, refer to Gotto and Opie.[47] *(Based on the current European Society of Cardiology guidelines for overt CHD.)*

proposed site of interaction being at the level of gastrointestinal hormones.[23]

Is it all too complex?

There are so many food and dietary choices, each with arguments in their favour, that our personal choice has been simplified to: 'All the colours every day', a brief but compelling message from an Italian nutritionist.

Evaluation of statin therapy

Statins: Benefits predominate

There is no doubt that statins are effective in secondary prevention, e.g. after an acute coronary syndrome (ACS); however, a steep linear relationship exists between LDL-C levels and the 10-year CHD risk (Fig. 3). Thus, the higher the initial LDL-C, the greater the statin-induced reduction of CHD events. Under-dosing statin in this setting is a frequent error; doses should be at the upper end of the dose range to obtain maximal cardioprotection.[24]

The benefit of statins is less in primary prevention. Even at very high LDL-C levels (e.g. 5 mmol/l), the 10-year risk is only close to 5% (Fig. 3). Statins affect a risk reduction of about one-fifth for every 1 mmol/l drop in LDL-C.[25] Therefore, statins can reduce this risk by almost half. However, the closer the untreated LDL-C gets to 2.5 mmol/l, a threshold often recommended for introducing statin therapy, the less the absolute benefit, even though the *relative* cardiovascular benefit, expressed as the percentage decrease in risk, remains constant.

Current ACC/AHA guideline recommendations

Almost all patients with prior ACS events, and/or clinical atherosclerotic cardiovascular disease (ASCVD) or otherwise judged to be at high risk, such as those with diabetes, require a statin for secondary prevention. For primary prevention, the 2013 ACC/AHA guideline recommendations for statin therapy cover are LDL-C in the range 1.8 - 4.8 mmol/l (Table 2).[1] Higher LDL-C levels may need exclusion of hereditary lipid problems by a lipidologist.

The four major groups that have been shown to derive benefit from statins are those:

- with clinical ASCVD, in patients <75 years of age
- with primary elevation of LDL-C of ≥4.9 mmol/l
- with diabetes, in patients aged 40 - 75 years with an LDL-C of 1.8 - 4.8 mmol/l, but without ASCVD
- without *clinical* ASCVD or diabetes with an LDL-C of 1.8 - 4.8 mmol/l and an estimated 10-year risk of ASCVD ≥7.5%

South African guidelines

The South African guidelines,[26] based on those of the European Society of Cardiology (ESC), recommend the assessment of risk in primary prevention using the updated Framingham risk charts. The four categories of the Framingham risk score refer to the 10-year risk of any cardiovascular event. For the highest risk group (>30%), the LDL-C goal is 1.8 mmol/, for the 15 - 30% risk group it is 2.5 mmol/l, and for <15% risk the goal is 3 mmol/l.[26]

Risk prediction is no easy matter

Accurate risk prediction is difficult, whether the ACC/AHA or the ESC guidelines are used. A recent *Lancet* editorial pointed out that the levels of risk prediction by the new ACC/AHA guidelines are roughly double those observed in several major outcome trials, including the Women's Health Study, the Physicians' Health Study and the Women's Health Initiative Observational Study (Fig. 1). Thus, up to 50% of Americans apparently targeted by their new guidelines do not actually have a risk that exceeds 7.5%.[27]

Table 2. The major current ACC/AHA guidelines[1] for statin indications taking the level of evidence into account

A. Must give

Class of recommendation I, level of evidence A:

- Persons <75 years of age with clinical ASCVD, give high intensity dose; if not tolerated, give moderate dose
- Persons 40 - 75 years of age with DM, without ASCVD and with an LDL-C 1.8 - 4.8 mmol/l, give moderate dose (Fig. 2)
- Primary prevention in adults 45 - 75 years of age, without ASCVD or DM and estimated 10-year ASCVD risk of ≥7.5% (Fig. 2)

B. Reasonable to give

Class of recommendation I, level of evidence B:

- Primary prevention in patients ≥21 years of age with an LDL-C ≥4.9 mmol/l; high dose, or if not tolerated, moderate dose
- Primary prevention in patients ≥21 years of age with an LDL-C 1.8 - 4.8 mmol/l and 10-year risk of ≥7.5%
- Genetic predisposition: No clear recommendation but include genetically high LDL-C ≥4.1 mmol/l, strong family history

Class of recommendation IIA, level of evidence B:

- Patients ≥75 years of age with clinical ASCVD after considering the potential benefit v. potential adverse effects, drug-drug interactions and personal preference; give moderate to high dose

ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol.

The most recent approach, derived from the Treating to New Targets (TNT) trial (*N*=10 001), gives *13 easy-to-measure clinical predictors*: age; sex; smoking; diabetes mellitus; total cholesterol; HDL-C; systolic BP; history of myocardial infarction; coronary artery bypass grafting; congestive heart failure or abdominal aortic aneurysm; glomerular filtration rate; and treatment status (low- (10 mg) or high-dose (80 mg) atorvastatin).[28] When applying these factors in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial (*N*=8 888), the model identified a group of 11.7% whose predicted 5-year number needed to treat (NNT) was ≤25 and a group of 41.9% whose predicted NNT was ≥50.[28] Of note, however, peripheral artery disease and stroke were not included.

Should low-risk CVD patients take a statin?

This remains an unresolved issue, the problem being that in clinical practice the level of risk is decided largely by the levels of LDL-C and not by clear clinical criteria. The current Cochrane review supports statin use for primary prevention even in patients at risk levels <10%.[29] The review found reductions in all-cause mortality, major vascular events and revascularisations with no excess of adverse events among people without evidence of CVD treated with statins. These data make a strong case for statins in primary prevention in selected patients with risk rates that merit therapy (see section on risk prediction).

Could additional tests help the decision?

Supporting the current concept that vascular inflammatory changes are fundamental to the development of atherosclerosis,[24] months of potent statin therapy reduced C-reactive protein (CRP) levels in association with decreased major adverse coronary events.[30] Thus, inflammation may be an important driver of residual cardiovascular risk in patients with coronary artery disease despite aggressive statin therapy. The advantage for South African doctors is that high-sensitivity CRP and apolipoprotein a can be measured easily.[26] In exceptional cases the accuracy of risk prediction may be improved by imaging techniques such as carotid ultrasound, coronary calcium scoring or computed tomography coronary angiography, which may detect preclinical atherosclerosis and thereby support the need for treatment.[26]

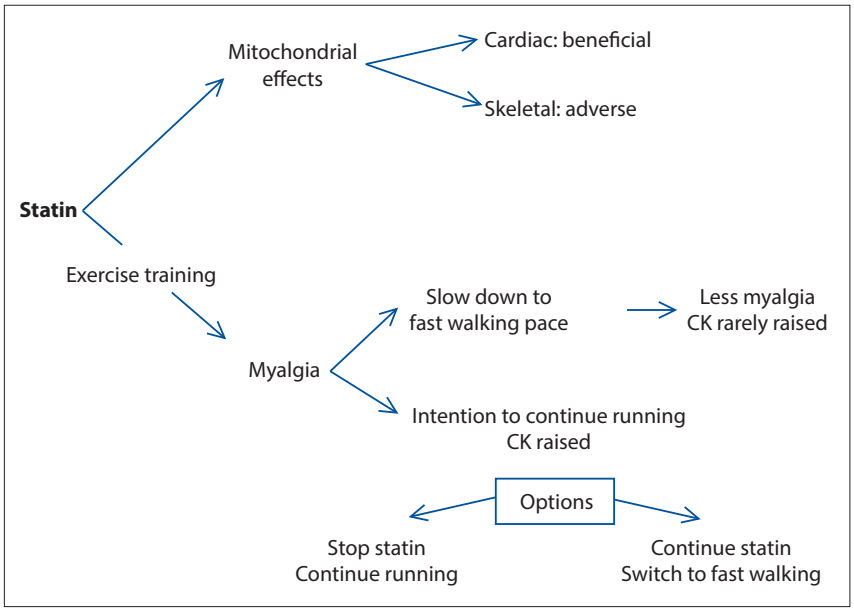

Fig. 4. Suggested algorithm for runners developing myalgia. For advantages of walking fast and intensely, refer to Jukema et al.[39] (CK = creatine kinase.)

Statin side-effect: Memory lost or improved?

An anguished patient cried out: 'Several people I know had terrible leg cramps when they took statins. I also read in the paper that statins can cause memory loss. My doctor wants me to start taking statins, but I'm scared. How real are these concerns?'[31] According to the Cochrane review,[29] few side-effects should be anticipated. However, two that often concern patients are memory loss and, especially in exercising patients, myalgia.

At least some degree of memory loss is inevitable in the age group of many persons taking statins. Data from the large randomised controlled trials assessing the development of

Table 3. Interaction between varying degrees of exercise-induced fitness and statin treatment on mortality rates in dyslipidaemic US veterans[11]*

Category	Total, *N*	MET† group	Deaths, %	HR unadjusted	HR fully adjusted	*p*-value‡
Least fit						
No statin	1 024	≤5.0	52	1.22	1.35	<0.0001
Statin	1 060	≤5.0	37	1.0	1.0	-
Moderately fit						
No statin	1 154	5.1 - 7.0	34	0.81	1.02	0.81§
Statin	1 573	5.1 - 7.0	21	0.57	0.65	<0.0001
Fit						
No statin	1 335	7.1 - 9.0	20	0.50	0.81	0.01
Statin	1 705	7.1 - 9.0	10	0.28	0.41	<0.0001
Highly fit						
No statin	1 498	>9.0	13	0.27	0.53	<0.0001
Statin	694	>9.0	6	0.16	0.30	<0.0001

MET = metabolic equivalent of task; HR = hazard ratio.
*Data from Kokkinos *et al.*[10] (Tables 3 and 4).
†Measure of energy expenditure; 1 MET is the amount of energy required to sit quietly.
‡*p*-value for fully adjusted HRs.
§*p*-value not significant.

Alzheimer's disease and memory loss are not yet available. Though initial analyses indicate that statins do not prevent Alzheimer's disease, they have a significant beneficial effect on the mini-mental state 30-point questionnaire test used to screen for cognitive impairment.[32] A meta-analysis of 16 studies focused on short- and long-term cognitive effects of statins found no short-term benefit with suggestion of a long-term benefit in preventing dementia.[33] The anti-inflammatory effects of statins provide a plausible mechanism for these statin effects.[34]

Statin side-effect: Myalgia

Prominent among the statin side-effects are myalgia and muscular weakness, which may be associated with a rise in circulating creatine kinase (CK).[35] In order of increasing severity and decreasing incidence, the statin-induced muscle-related conditions are myalgia, myopathy with elevated CK levels with or without symptoms, and rhabdomyolysis. Statins may increase CK levels without decreasing average muscle strength or exercise performance. In one large study, only about 2% had myalgia that could be attributed to statin use.[35] At a cellular level, statins optimise cardiac mitochondrial function but impair skeletal mitochondrial function by inducing different levels of reactive oxygen species at these two sites. The level of exercise and/or dose of statin may need reduction if the severity of the pain is limiting exercise (Fig. 4). Coenzyme Q10 has no proven benefit.[35]

Myalgia should be balanced against the positive health benefits of statins beyond the cardiovascular, which include decreased adverse events in heart failure patients,[36] decreased atrial fibrillation, modest antihypertensive effects and reduced risks of malignancies.[35]

Statins and new-onset diabetes

The four major risk factors for developing diabetes are: metabolic syndrome; impaired fasting glucose; body mass index (BMI) ≥30 kg/m^2 and glycated haemoglobin A1c >6%.[37] In a 5-year trial (*N*=17 603) in those with one or more risk factors, the use of 20 mg rosuvastatin daily was associated with a 39% reduction in the first occurrence of a major cardiovascular event (hazard ratio (HR) 0.61; *p*=0.0001) and a 28% increase in diabetes (HR 1.28; 95% confidence interval (CI) 1.07 - 1.54; *p*=0.01).[37]

Overall, considering all statins, in 13 trials (*N*=91 140) statin therapy was associated with a 9% (95% CI 1.02 - 1.17) increased risk for incident diabetes.[38] Treatment of 255 patients with statins for 4 years resulted in only one extra case of diabetes.[38] This small absolute risk for new diabetes is more than outweighed by cardiovascular benefits.[39] Thus, in 17 080 patients high-dose statin therapy over 5 years decreased ACS or death by 45% at the cost of 13.3% new-onset diabetes.[40]

Most importantly, new-onset diabetes can be avoided if the patient has none or only 1/4 risk factors for new diabetes: fasting blood glucose >5.5 mmol/l; fasting triglycerides >1.7 mmol/l; BMI >30 kg/m^2; and a history of hypertension. In those with 2 - 4 of these adverse factors, new-onset diabetes developed in 14%.[41]

Which statins are least likely to cause new diabetes? Compared with pravastatin, which was not associated with new diabetes, the absolute risks were 26, 31 and 34 events per 1 000 years of therapy, respectively, for simvastatin, atorvastatin and rosuvastatin.[42] These are remarkably low risks.

Statins in renal disease

In patients with chronic kidney disease, including those receiving dialysis, statins reduce the risk of major cardiovascular events.[43]

Lifestyle plus statins: Do they go together?

This is an ideal combination for those with high LDL-C levels that do not respond to lifestyle changes alone or for those who have not received or are unlikely to follow advice about making lifestyle changes. For some, if not many, patients it may be easier to take one or two tablets each day than to find the time and determination to exercise regularly. Despite this, the attending medical practitioner should strongly recommend combining statins with lifestyle changes, including exercise.

In an observational study, both statins and exercise individually reduced the adverse outcomes of CVD. Their combined effects were additive (Table 3). In the least physically fit, no statin group, baseline total cholesterol was 6.0 mmol/l, with baseline LDL-C being

4 mmol/l. After statin treatment, total cholesterol was 4.1 mmol/l, and LDL-C was 2.6 mmol/l ($p<0.0001$). Before intense exercise, lipids levels were similar. After intense exercise training, values were: total cholesterol 5.1 mmol/l, with LDL-C being 3.6 mmol/l. The combination of high fitness (for definition, refer to Lee and Paffenbarger[45]) and statin treatment in patients yielded a substantial reduction in mortality risk than in those who were least fit and either taking statin or no statin (HR 0.30; $p<0.0001$).

The major unresolved problem is that either exercise or statins can singly cause muscular symptoms with an elevation of serum CK.[35] There is, as yet, no clearly defined outcomes-based policy to deal with such symptoms. A reasonable practical approach is to assess the CK level, and if elevated, to reduce either the statin dose or the intensity of exercise to brisk walking (Fig. 4).[44,45]

Conclusion

Both lifestyle changes and statin therapy and their combination have well-defined positive roles in the management of the patient who needs advice on cardiovascular health.

Acknowledgements. We thank Proff M Ntsekhe and P J Commerford, Department of Cardiology, Groote Schuur Hospital, Cape Town, South Africa for their helpful comments.

References

1. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013. [http://dx.doi.org/10.1161/01.cir.0000437738.63853.7a]
2. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: Benefits among users and nonusers of lipid-lowering and antihypertensive medications. Circulation 2006;114(2):160-167. [http://dx.doi.org/10.1161/CIRCULATIONAHA.106.621417]
3. Chiuve SE, Rexrode KM, Spiegelman D, Logroscino G, Manson JE, Rimm EB. Primary prevention of stroke by healthy lifestyle. Circulation 2008;118(9):947-954. [http://dx.doi.org/10.1161/CIRCULATIONAHA.108.781062]
4. Van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: Prospective cohort study in US women. BMJ 2008;337:a1440. [http://dx.doi.org/10.1136/bmj.a1440]
5. Dong C, Rundek T, Wright CB, Anwar Z, Elkind MS, Sacco RL. Ideal cardiovascular health predicts lower risks of myocardial infarction, stroke, and vascular death across whites, blacks, and hispanics: The northern Manhattan study. Circulation 2012;125(24):2975-2984. [http://dx.doi.org/10.1161/CIRCULATIONAHA.111.081083]
6. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392-2404. [http://dx.doi.org/10.1056/NEJMoa1014296]
7. Yates T, Haffner SM, Schulte PJ, et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): A cohort analysis. Lancet 2013. [http://dx.doi.org/10.1016/S0140-6736(13)62061-9]
8. Piepoli MF, Davos C, Francis DP, Coats AJ; ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004;328:189-196. [http://dx.doi.org/10.1136/bmj.37938.654220.EE]
9. Posel D, Noakes T, Kantor P, Lambert M, Opie LH. Exercise training after experimental myocardial infarction increases the ventricular fibrillation threshold before and after the onset of reinfarction in the isolated rat heart. Circulation 1989;80(1):138-145. [http://dx.doi.org/10.1161/01.CIR.80.1.138]
10. Noakes TD, Opie LH, Rose AG, Kleynhans PH, Schepers NJ, Dowdeswell R. Autopsy-proved coronary atherosclerosis in marathon runners. N Engl J Med 1979;301(2):86-89. [http://dx.doi.org/10.1056/NEJM197907123010205]
11. Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: A cohort study. Lancet 2013;381:394-399. [http://dx.doi.org/10.1016/S0140-6736(12)61426-3]
12. Kujala UM, Mäkinen VP, Heinonen I, et al. Long-term leisure-time physical activity and serum metabolome. Circulation 2013;127(3):340-348. [http://dx.doi.org/10.1161/CIRCULATIONAHA.112.105551]
13. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364(25):2392-2404. [http://dx.doi.org/10.1056/NEJMoa1014296]
14. Shai I, Schwarzfuchs D, Henkin Y, et al; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359(3):229-241. [http://dx.doi.org/10.1056/NEJMoa070868]
15. Noakes TD, Creed S-A, Proudfoot J, Grier D. The Real Meal Revolution. Cape Town: Quivertree Publications, 2013.
16. Noakes M, Foster PR, Keogh JB, James AP, Mamo JC, Clifton PM. Comparison of isocaloric very low carbohydrate/high saturated fat and high carbohydrate/low saturated fat diets on body composition and cardiovascular risk. Nutr Metab (Lond) 2006;3:7. [http://dx.doi.org/10.1186/1743-7075-3-7]
17. Noakes TD. Low-carbohydrate and high-fat intake can manage obesity and associated conditions: Occasional survey. S Afr Med J 2013;103(11):826-830. [http://dx.doi.org/10.7196/SAMJ.7302]
18. Poulsen SK, Due A, Jordy AB, et al. Health effect of the New Nordic Diet in adults with increased waist circumference: A 6-mo randomized controlled trial. Am J Clin Nutr 2014;99(1):35-45. [http://dx.doi.org/10.3945/ajcn.113.069393]
19. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348(26):2599-2608. [http://dx.doi.org/10.1056/NEJMoa025039]
20. Estruch R, Ros E, Salas-Salvadó J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet N Engl J Med 2013;368:1279-1290. [http://dx.doi.org/10.1056/NEJMoa1200303]
21. Opie LH. Mediterranean diet for primary prevention of cardiovascular disease. N Engl J Med 2013;369:672-677. [http://dx.doi.org/10.1056/NEJMc1306659]
22. Bao Y, Han J, Hu FB, et al. Association of nut consumption with total and cause-specific mortality. N Engl J Med 2013;369:2001-2011. [http://dx.doi.org/10.1056/NEJMoa1307352]
23. Shaodong C, Haihong Z, Manting L, Guohui L, Zhengxiao Z, Zhang YM. Research of influence and mechanism of combining exercise with diet control on a model of lipid metabolism rat induced by high fat diet. Lipids Health Dis 2013;12:21. [http://dx.doi.org/10.1186/1476-511X-12-21]
24. Arnold SV, Spertus JA, Masoudi FA, et al. Beyond medication prescription as performance measures: Optimal secondary prevention medication dosing after acute myocardial infarction. J Am Coll Cardiol 2013;62(19):1791-1801. [http://dx.doi.org/10.1016/j.jacc.2013.04.102]
25. Baigent C, Keech A, Kearney PM, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366(9493):1267-1278. [http://dx.doi.org/10.1016/S0140-6736(05)67394-1]
26. Klug E; South African Heart Association (S A Heart); Lipid and Atherosclerosis Society of Southern Africa (LASSA). South African Dyslipidaemia Guideline Consensus Statement. S Afr Med J 2012;102(3):178-187.
27. Ridker PM, Cook NR. Statins: New American guidelines for prevention of cardiovascular disease. Lancet 2013;382(9907):1762-1765. [http://dx.doi.org/10.1016/S0140-6736(13)62388-0]
28. Dorresteijn JA, Boekholdt SM, van der Graaf Y, et al. High-dose statin therapy in patients with stable coronary artery disease: Treating the right patients based on individualized prediction of treatment effect. Circulation 2013;127(25):2485-2493. [http://dx.doi.org/10.1161/CIRCULATIONAHA.112.000712]
29. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013;1:CD004816. [http://dx.doi.org/10.1002/14651858.CD004816.pub5]
30. Puri R, Nissen SE, Libby P, et al. C-reactive protein, but not low-density lipoprotein cholesterol levels, associate with coronary atheroma regression and cardiovascular events after maximally intensive statin therapy. Circulation 2013;128(22):2395-2403. [http://dx.doi.org/10.1161/CIRCULATIONAHA.113.004243]
31. Heart Advisor. October 2008. http://www.heart-advisor.com/issues/11_10/ (accessed 31 January 2014).
32. McGuinness B, Passmore PJ. Can statins prevent or help treat Alzheimer's disease? Alzheimers Dis 2010;20(3):925-933. [http://dx.doi.org/10.3233/JAD-2010-091570]
33. Swiger KJ, Manalac RJ, Blumenthal RS, et al. Statins and cognition: A systematic review and meta-analysis of short- and long-term cognitive effects. Mayo Clin Proc 2013;88(11):1213-1221. [http://dx.doi.org/10.1016/j.mayocp.2013.07.013]
34. Tendolkar I, Enajat M, Zwiers MP, et al. 1-year cholesterol lowering treatment reduces medial temporal lobe atrophy and memory decline in stroke-free elderly with atrial fibrillation: Evidence from a parallel group randomized trial. Int J Geriatr Psychiatry 2012;27(1):49-58. [http://dx.doi.org/10.1002/gps.2688]
35. Opie LH. Exercise-induced myalgia may limit the cardiovascular benefits of statins. Cardiovasc Drugs Ther 2013;27(6):569-572. [http://dx.doi.org/10.1007/s10557-013-6483-8]
36. Correale M, Totaro A, Passero T, et al. Treatment with atorvastatin is associated with a better prognosis in chronic heart failure with systolic dysfunction: Results from the Daunia Heart Failure Registry. Neth Heart J 2013;21(9):408-416. [http://dx.doi.org/10.1007/s12471-013-0430-y]
37. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: An analysis from the JUPITER trial. Lancet 2012;380(9841):565-571. [http://dx.doi.org/10.1016/S0140-6736(12)61190-8]
38. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. Lancet 2010;375(9716):735-742. [http://dx.doi.org/10.1016/S0140-6736(09)61965-6]
39. Jukema JW, Cannon CP, de Craen AJ, Westendorp RG, Trompet S. The controversies of statin therapy: Weighing the evidence. J Am Coll Cardiol 2012;60(10):875-881. [http://dx.doi.org/10.1016/j.jacc.2012.07.007]
40. Ko DT, Wijeysundera HC, Jackevicius CA, et al. Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins. Circ Cardiovasc Qual Outcomes 2013;6(3):315-322. [http://dx.doi.org/10.1161/CIRCOUTCOMES.111.000015]
41. Waters DD, Ho JE, Boekholdt SM, et al. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: Effect of baseline risk factors for diabetes. J Am Coll Cardiol 2013;61(2):148-152. [http://dx.doi.org/10.1016/j.jacc.2012.09.042]
42. Carter AA, Gomes T, Camacho X, et al. Risk of incident diabetes among patients treated with statins: Population based study. BMJ 2013;346:f2610. [http://dx.doi.org/10.1136/bmj.f2610]
43. Hou W, Lv J, Perkovic V, Yang L, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: A systematic review and meta-analysis. Eur Heart J 2013;34(24):1807-1817. [http://dx.doi.org/10.1093/eurheartj/eht06]
44. Schnohr P, Scharling H, Jensen JS. Intensity versus duration of walking, impact on mortality: the Copenhagen City Heart Study. Eur J Cardiovasc Prev Rehabil 2007;14(1):72-78. [http://dx.doi.org/10.1097/HJR.0b013e3280144470]
45. Lee IM, Paffenbarger RS Jr. Associations of light, moderate, and vigorous intensity physical activity with longevity: The Harvard Alumni Health Study. Am J Epidemiol 2000;151(3):293-299. [http://dx.doi.org/10.1093/oxfordjournals.aje.a010205]
46. Opie LH. Living Longer, Living Better. Exploring the Heart-Mind Connection. Oxford: Oxford University Press, 2011:36.
47. Gotto A Jr, Opie LH. Lipid-modifying and anti-atherosclerotic drugs. In: Opie LH, Gersh BJ, eds. Drugs for the Heart. 7th ed. Philadelphia: Elsevier Saunders, 2009:353.

Accepted 16 January 2014.