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REVIEW

Primary Prevention of Coronary Artery Disease

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Abstract

There were an estimated one million deaths from cardiovascular disease in sub-Saharan Africa in 2013. The deaths can in some part be prevented through the control of risk factors for coronary artery disease. The major modifiable risk factors in adults include: smoking, obesity, unhealthy diet, dyslipidaemia, hypertension and diabetes. This article aims to discuss the primary prevention of coronary artery disease through examining the evidence regarding the control of these modifiable risk factors. It also briefly explains a pragmatic approach to the use of aspirin as primary prevention for coronary artery disease which takes into account both the risks and benefits associated with aspirin use.

Keywords: cardiovascular risk factors, primary prevention, aspirin therapy, dyslipidaemia.

Introduction

In 2013, there were an estimated 1 million deaths that were attributable to cardiovascular disease (CVD) in sub-Saharan Africa, which constituted approximately 5.5% of all global cardiovascular disease-related deaths and 11.3% of deaths in Africa.[1,2] This means that cardiovascular-related death made up 38% of all non-communicable disease-related deaths in Africa, which reflects a growing threat of both non-communicable disease and CVD.[1,2] The majority of risk factors for coronary artery disease (a cause of cardiovascular disease) and stroke are modifiable by preventative measures, including therapeutic and adjunctive therapies.[3]

Major Modifiable Risk Factors for Coronary Artery Disease (CAD)

The INTERHEART study of patients from 52 countries, demonstrated that there were 9 potentially modifiable risk factors which accounted for over 90% of the population attributable risk of a myocardial infarction.[4] The major modifiable risk factors are detailed in Table 1.[4] The potentially deleterious consequences of multiple risk factors are additive at the very least.[5]

Table 1: Major for modifiable risk factors for coronary artery disease (CAD)[4]

The following major risk factors for coronary artery disease are modifiable and should be considered in all adults:
1. Smoking
2. Overweight and obesity
3. Unhealthy diet
4. Sedentary lifestyle
5. Dyslipidaemia
6. Hypertension
7. Diabetes (considered in some guidelines as coronary artery disease risk equivalents)

Smoking avoidance or Cessation

Cigarette smoking remains the leading cause of premature death and a major avoidable cause of premature disability. The evidence indicates that the number of cigarettes currently smoked increases morbidity and mortality from CVD, and the benefits of smoking cessation begin to appear only after a few months of successful cessation and take several years to reach that of a non-smoker, even among adults under the age of 65 years.[6] The benefits of smoking cessation are detailed in Table 2.[7,8]

Table 2: Health Benefits of Smoking Cessation

The benefits of smoking cessation include:
Decreased risk of myocardial infarctions or strokes
Decreased blood pressure
Decreased risk of developing Peripheral Artery Disease (PAD)
Decreased cholesterol
Decreased risk of pulmonary disorders (COPD or lung cancer)

It is with this in mind that we as healthcare professionals should always suggest smoking cessation to our patients.[7,8] The type of healthcare professional delivering the counselling regarding smoking cessation is not as important as the message being delivered consistently and correctly by multiple healthcare professionals involved in the patient's care.[8] The DESMOND study conducted in patients with newly diagnosed type 2 diabetes demonstrated that structured education can result in higher rate of smoking cessation after a period of 12 months,[9] but this effect is lost after 3 years.[10] A number of treatment approaches may be required to produce smoking cessation. These include behavioural intervention, the use of nicotine replacement therapy and pharmacotherapy using bupropion and varenicline.[8]

Overweight and Obesity

Being overweight or obese increases several modifiable risk factors for coronary artery disease, including diabetes, hypertension and dyslipidaemia.[11,12] At every encounter a patient's weight should be measured and their BMI should be calculated.[13] The patients waist circumference should be measured as well to determine the presence of abdominal obesity especially if the BMI is < 35 kg/m^2. Among overweight and obese patients analysis has demonstrated that the greater the BMI the higher the risk of fatal coronary artery disease (CAD) as well as combined fatal and nonfatal coronary artery disease.[13]

A 5% weight reduction in overweight and obese patients produces a weighted mean reduction in systolic and diastolic blood pressure of approximately 3 and 2 mmHg respectively. Furthermore, a 5 to 8 kg loss in weight reduces the low-density lipoproteins (LDL-C) cholesterol, the triglycerides and increases the high-density lipoprotein cholesterol (HDL-C). The target should thus be to produce a 5 to 10% weight loss gradually over a period of 6 months through a calorie restricted diet of approximately 1200 to 1500 kcal/day in women and 1500 to 1800 kcal/day in men. This will produce an energy deficit of between 500 and 750 kcal/day. A variety of dietary approaches can be used to produce weight loss.[13] Practitioners should preferably refer patients to an expert dietician who can work with the patient on a diet that best suits their lifestyle.[13] Diet should be combined with physical activity as part of a regular and intensive lifestyle intervention programme, both of which will be discussed in more detail in the upcoming sections. Whilst intensive lifestyle interventions designed to produce weight loss have not resulted in reduced risk for CVD in patient with diabetes, the Look AHEAD trial demonstrated that patients with type 2 diabetes who underwent intensive lifestyle interventions were able to produce equivalent risk factor control (compared to the standard of care) with fewer blood pressure-, glucose- and lipid-lowering medications.[7,14] Table 3 indicates the BMI cut-off at which different treatment options are indicated.[7] The American Diabetes Association (ADA) has suggested that the BMI cut-off should be 2.5 kg/m^2 lower for Asians and those of Asian descent.[7]

Pharmacotherapy for obesity includes liraglutide, orlistat or the combination of phentermine and topiramate. The long-term use of these agents is not advised, and treatment discontinuation is recommended if weight loss is less than 5% in 3 months. Table 4 illustrates an overview of pharmacotherapy that can be used in the management of obesity.

Diet and Exercise

Patients who self-select for a healthy diet have a significantly lower risk of cardiovascular disease including coronary artery disease and stroke.[20] Table 5 indicates the components of the healthy diet.

Table 5: Components of a healthy diet[13,21]

The components of a healthy diet include intakes of:
Fruits and vegetables
High fibre intake
Foods with a low glycaemic index and low glycaemic load
Monounsaturated fats
Omega-3 fatty acids from dietary sources especially fish

Table 3: Treatment options for overweight or obese patients[7]

Treatment	**BMI Category (kg/m^2)**				
	25.0–26.9 Or 23.3–26.9 for Asians	**27.0–29.9**	**30.0–34.9 OR 27.5–32.4 for Asians**	**35.0–39.9 OR 32.5–37.4 for Asians**	**≥ 40 OR ≥ 37.5 for Asians**
Diet, physical activity and behavioural therapy	I	I	I	I	I
Pharmacotherapy	NI	I	I	I	I
Bariatric Surgery	NI	NI	I	I	I

Key: NI – Not Indicated; I – Indicated for selected for motivated patients

Table 4: Overview of pharmacotherapy used in the management of obesity[7,15-19]

Drug Name	**Usual Adult Dosage**	**1 year weight Status Change**		**Adverse Effect**	
		Average weight loss relative to Placebo	**% of Patients with ≥ 5% weight loss from baseline**	**Common**	**Serious**
Phentermine/ topiramate	3.75 mg/23 mg daily for 14 days, increasing to 7.5 mg/ 46 mg daily with a maximum dose of 15 mg/92 mg daily	8.8 kg	45–70%	Paraesthesia, xerostomia, constipation, headache	Topiramate is teratogenic and can cause cleft lips/palates
Orlistat	120 mg three times daily or 60 mg three times daily	2.5 kg for 60 mg or 3.4 kg for 120 mg	35–73%	Soft stools, abdominal pain or colic, flatulence, faecal urgency, or incontinence has been reported in up to 80% of individuals using 120 mg of orlistat	Liver failure and oxalate neuropathy
Liraglutide	3 mg SC daily	5.3 kg	51–73%	Hypoglycaemia, nausea, vomiting, diarrhoea, constipation, headache	Pancreatitis, thyroid C-cell tumours in rats

Observational studies have consistently demonstrated that individuals consuming a diet high in fruits and vegetables like that of the Mediterranean diet have a reduced risk of CVD.[22,23] In overweight and obese adults the Mediterranean diet, low glycaemic load diet and low glycaemic index diet produce cardiovascular benefits that are comparable to an energy restricted low-fat diet.[13] A recently published meta-analyses demonstrated that marine-derived omega-3 fatty acids supplements had no significant association with reductions in fatal or nonfatal coronary artery disease risk.[24]

There seems to be an inverse relationship between CVD and exercise meaning that the more exercise a patient does, the less likely they are to experience a cardiovascular event or CVD mortality.[25] Systematic reviews and meta-analyses have consistently demonstrated that physical activity reduces the risk of CVD and strokes in both men and woman.[26,27,28] Most of these studies used validated self-reported physical activity/exercise measures and had well documented and reliable CVD incidence and mortality measures which added to their validity.[25] Table 6 illustrates the evidence based recommendations regarding the use of exercise to reduce the risk of CAD.[13,29-31]

Table 6: Evidence-based recommendations regarding the use of exercise to reduce coronary artery disease (CAD) risk[13,29-31]

The following are common recommendations for physical activity in adults:
1. Adults should perform 2.5 hours of moderate intensity exercise per week. Examples of such exercise includes: a. brisk walking b. swimming c. cycling
2. An alternative to this is the performance of 75 minutes of vigorous intensity exercise per week
3. In overweight and obese patients, the recommendation of 2.5 hours per week to produce weight loss still stands, but higher levels of physical activity/exercise of approximately 3 to 5 hours per week are recommended for weight maintenance.
4. Modest amounts of physical activity such as brisk walking for 20 minutes per day are still associated with significant benefits in reducing coronary artery disease risk.

Table 7: Updated Framingham CVD risk tables for men and women

Estimate of 10-year risk of CVD for men		**Estimate of 10-year risk of CVD for women**	
Age (yrs)	**Points**	**Age (yrs)**	**Points**
30–34	0	30–34	0
35–39	2	35–39	2
40–44	5	40–44	4
45–49	6	45–49	5
50–54	8	50–54	7
55–59	10	55–59	8
60–64	11	60–64	9
65–69	12	65–69	10
70–74	14	70–74	11
≥ 75	15	≥ 75	12
Total Cholesterol (mmol/l)	**Points**	**Total Cholesterol (mmol/l)**	**Points**
< 4.10	0	< 4.10	0
4.10–5.19	1	4.10–5.19	1
5.20–6.19	2	5.20–6.19	3
6.20–7.20	3	6.20–7.20	4
> 7.20	4	> 7.20	5
HDL-cholesterol (mmol/l)	**Points**	**HDL-cholesterol (mmol/l)**	**Points**
≥ 1.50	-2	≥ 1.50	-2
1.30–1.49	-1	1.30–1.49	-1
1.20–1.29	0	1.20–1.29	0
0.90–1.19	1	0.90–1.19	1
< 0.90	2	< 0.90	2
Systolic BP- untreated (mmHg)	**Points**	**Systolic BP- untreated (mmHg)**	**Points**
< 120	-2	< 120	-3
120–129	0	120–129	0
130–139	1	130–139	1
140–159	2	140–149	2
≥ 160	3	150–159	4
		≥ 160	5
Systolic BP- on antihypertensive treatment (mmHg)	**Points**	**Systolic BP- on antihypertensive treatment (mmHg)**	**Points**
< 120	0	< 120	-1
120–129	2	120–129	2
130–139	3	130–139	3
140–159	4	140–149	5
≥ 160	5	150–159	6
		≥ 160	7
Smoker	**Points**	**Smoker**	**Points**
No	0	No	0
Yes	4	Yes	3

Dyslipidaemia

Large-scale randomised controlled trials and their meta-analyses of statins in high-, moderate- and low-risk individuals without clinical evidence of CAD have demonstrated clinical benefits on CVD, including myocardial infarctions (MI), strokes and other CVD related mortalities.[32] Deciding on whom to screen for dyslipidaemia should be dependent on the guidelines utilised. The South African guidelines for Dyslipidaemia suggest all adults over the age of 20 years should be screened at least once for the presence of dyslipidaemia.[33] The use of the Framingham risk score system has been proposed in these guidelines. It is important to remember, however, that the tables used to derive the Framingham risk scores (See Tables 7 and 8) may underestimate the coronary heart disease risk in the South African Black and Indian population.[33] Table 7 illustrates the Framingham risk tables for both men and women.

Table 8 illustrates the conversion of the points to 10-year risk percentage of cardiovascular risk.

Table 8: Conversion of the points to 10-year risk percentage of cardiovascular risk

Points total for men		Points total for women	
Points total	**10 year risk (%)**	**Points total**	**10 year risk (%)**
-3 or less	< 1	-2 or less	< 1
-2	1.1	-1	1.0
-1	1.4	0	1.1
0	1.6	1	1.5
1	1.9	2	1.8
2	2.3	3	2.1
3	2.8	4	2.5
4	3.3	5	2.9
5	3.9	6	3.4
6	4.7	7	3.9
7	5.6	8	4.6
8	6.7	9	5.4
9	7.9	10	6.3
10	9.4	11	7.4
11	11.2	12	8.6
12	13.2	13	10.0
13	15.6	14	11.6
14	18.4	15	13.5
15	21.6	16	15.6
16	25.3	17	18.1
17	29.4	18	20.9
18 or more	> 30	19	24.0
		20	27.5
		20 or more	> 30

The percentages are grouped into categories of low risk, moderate risk, high risk or very high risk (See Table 9). These risk categories are then used to determine the intervention as required.

Table 9: Risk grading for 10-year risk of CVD based on sex

Men	Women
1. Low risk is **< 1–2.8%** 10-year risk of CVD	1. Low risk is **< 1–2.9%** 10-year risk of CVD
2. Moderate risk is **3.3–13.2%** 10-year risk of CVD	2. Moderate risk is **3.4–13.5%** 10-year risk of CVD
3. High risk is **15.6–29.4%** 10-year risk of CVD	3. High risk is **15.6–27.5%** 10-year risk of CVD
4. Very High risk is **> 30%** 10-year risk of CVD	4. Very High risk is **> 30%** 10-year risk of CVD

For those patients with an initial cardiovascular risk of < 3% and between 3 and 15%, the LDL-C goal should be < 3 mmol/l.[33] All patients with LDL-C levels high than 3 mmol/l should be placed on therapeutic lifestyle changes (TLC). Statin therapy should be instituted if LDL-C level of the patient consistently exceeds 4.9 mmol/l (despite lifestyle intervention) in those with a cardiovascular risk of < 3% or if LDL-C level consistently exceeds 3 mmol/l (despite lifestyle intervention) in patients with a CVD risk of between 3–15%.[33]

For patients with CVD risk of > 15% but < 30%, the LDL-C goal should be < 2.5 mmol/l.[33] Statin therapy should be instituted immediately in these patients if the LDL-C level exceeds 2.5 mmol/l and TLC as well as statins may be considered if the LDL-C of the patient is < 2.5 mmol/l.[33]

For patients with a CVD risk which exceeds 30%, the LDL-C goal for these patients should be < 1.8 mmol/l.[33] Patients should immediately be prescribed statin therapy and TLC to achieve the goal of < 1.8 mmol/l.[33]

The South African essential drugs list and standard treatment guidelines suggest that patients with 20% or more risk of an MI in ten years should be placed on a statin as these patients would benefit from such an intervention. The suggested statin should lower LDL-C by at least 25%, e.g. simvastatin 10 mg at night.[34]

Hypertension

Hypertension is defined as a systolic blood pressure (SBP) of ≥ 140 mmHg or a diastolic pressure (DBP) of ≥ 90 mmHg.[35] The goal of blood pressure management is to achieve a blood pressure of < 140 mmHg and < 90 mmHg. The non-pharmacological measures that can be used to achieve this include TLC such as: weight reduction, salt restrictions, smoking cessation and a reduction in alcohol intake.[35] Recently, the ACC/AHA and other organizations saw fit to reduce the definition of hypertension to a SBP of ≥ 130 mmHg and a DBP of ≥ 80 mmHg.[36] The rationale behind such a change was linked primarily to an increasing number of meta-analyses which demonstrated that the hazard ratio for CHD and stroke was between 1.5 and 2.0 for a SBP/DBP of 130–139/85–85 mmHg versus the normal blood pressure of < 120 and < 80 mmHg.[36–39] Whilst the recommendations of Whelton et al.[36] have yet to be adopted by the South African Hypertension Society, it is important to remember that patients with high normal blood pressure (i.e. SBP of 130–139 and DBP of 85–89) have a higher risk for both coronary artery disease and strokes when compared to those with normal blood pressure and thus lifestyle interventions must be instituted in this group.[35]

Patients with hypertension as classified under the current guidelines must be assessed for major CVD risk factors, complications and target organ damage before a decision is made on whether to begin pharmacotherapy.[35] All patients should be placed on TLC and where pharmacotherapy is required, the choices where there are no compelling indications include thiazide diuretics, ACE inhibitors or ARBs and long-acting dihydropyridine CCBs.[35]

Diabetes and Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT)

Diabetes is considered by some guidelines as a coronary artery disease risk equivalent.[7] Diabetes is associated with both macrovascular (CHD, stroke) and microvascular complications.[7] Whilst tight glycaemic control may also reduce the risk of macrovascular complications in both type 1 and type 2 diabetes, major CVD risk factors such as body weight, blood pressure and lipids must be controlled as an adjunct to glycaemic control.[7] The HbA1c goal for the patient with diabetes should be tailored to the individual by weighing the benefits on morbidity and mortality against the risk of hypoglycaemia.[7]

Both IFG and IGT are also risk factors for cardiovascular disease.[7,40] A recent meta-analysis of 53 prospective studies suggests that the relative risk (RR) for the primary cardiovascular composite outcome was higher for patients with IFG or IGT when compared to those with normoglycaemia.[40] This DECODE study also found a significantly increased risk of both all-cause and cardiovascular mortality in men with IGT.[41] The USS DPP, Finish DPS and the Da Qing study all provide good evidence to suggest that the first line treatment for either IFG or IGT should be intensive lifestyle interventions.[42-44] The key components of intensive lifestyle interventions are detailed in Table 10.[45]

Table 10: Key components of a successful lifestyle modification programme for patients with IFG or IGT[45]

1. Achieve and maintain weight loss > 5%
2. Modify dietary patterns that focus on:
2.2. Reducing energy from fat to < 30%
2.3. Reducing energy from saturated fat to ≤ 10%
2.4. Increasing fibre intake to ≥ 15 g/1000 kcal
3. Increase moderate intensity physical activity ≥ 150 minutes per week
4. Frequent contact and follow-up by the practitioner will improve intervention success

The prescription of pharmacotherapy for the management of IFG or IGT can be considered in select patients.[46] Table 11 provides an evidence Graded approach for prescribing pharmacotherapy in patients with IFG/IGT.[45]

Table 11: Evidence Graded approach for prescribing pharmacotherapy in patients with IFG/IGT[45]

Recommendation	Evidence Grade
Consider metformin in individuals who have deteriorating fasting plasma glucose (FPG) or 2-hour PG after 6 months, and: 1. Have participated in an intensive lifestyle modification programme 2. Have been unable to participate in an intensive intervention programme. Especially those who: 2.1 Are less than 60 years of age 2.2 Have history of gestational diabetes 2.3 Have a BMI > 35 kg/m^2 2.4 Have combined IFG and IGT 2.5 Have the metabolic syndrome These patients should be continuously supported with an intensive lifestyle modification programme.	A
Monitor IFG/IGT patients every 6–12 months and intensify lifestyle intervention and metformin doses if blood glucose doses do not improve. If metformin is not sufficient consider using an alternative drug, i.e. acarbose or orlistat.	B

Aspirin Therapy

Data from the meta-analysis by the US Preventative Services Task Force (USPSTF) has suggested that low dose aspirin produces a significant reduction in the relative risk for nonfatal MIs but not for nonfatal strokes.[46] The decision on whether to start aspirin therapy should be individualised based on the assessment of aspirin's effect on bleeding risk and the expected benefits as absolute bleeding risk may vary considerably by patient.[46] A pragmatic approach using the Framingham equation is detailed in Table 12.[47]

Table 12: A pragmatic evidence-based approach to the prescription of Aspirin as primary prevention using the patient's Framingham score.[47]

For moderate to high-risk patients whose 10-year absolute risk of a first CHD event is ≥ 10%, the randomised data on benefits and risks are sparse thus clinical decision making should be employed on an individualised basis to see if the benefits of using low dose aspirin to prevent a first MI are likely to exceed the risk of major bleeding.
For moderate to high risk patients whose 10-year absolute risk of a first CHD event is ≥ 10%, the randomised data on benefits and risks are sparse thus clinical decision making should be employed on an individualised basis to see if the benefits of using low dose aspirin to prevent a first BMI are likely to exceed the risk of major bleeding.

Conclusions

Primary prevention of coronary artery disease should focus to some degree on modifiable risk factor reduction. The common risk factors include: smoking, obesity, diet, sedentary lifestyle, dyslipidaemia, hypertension and diabetes. These factors may be controlled using either lifestyle interventions (a combination of diet and exercise) or a combination of lifestyle interventions and effective pharmacotherapy. The decision on whether to include aspirin therapy as primary prevention should be individualised to the patient in which aspirin is safe to be prescribed.

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