



Review Article

Cardiovascular Risk Factors and Its Management

Q T Islam¹, A R M Saifuddin Ekram², A S M Shawkat Ali³, M Ayub Ali⁴

Abstract

Major risk factors for cardiovascular diseases are hypertension, diabetes mellitus, dyslipidaemia, smoking and obesity. In this review article, we have tried to discuss the updated management of each major risk factor.

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Introduction

Cardiovascular risk factor is a condition that is associated with an increased risk of developing cardiovascular disease¹. It is not always obvious that person with one cardiovascular risk factor may develop the disease. But it increases the probability. On the contrary, person who does not have any risk factor may develop the cardiovascular disease². With rare exceptions, all heart attacks are caused by atherosclerosis of the coronary arteries resulting from fatty deposits called plaque³. Atherosclerosis also plays same

role in other vascular diseases like Stroke, Transient Ischemic Attack (TIA) and peripheral vascular diseases^{4,5}. Framingham heart study was the milestone study that revealed the cause of atherosclerotic heart disease. The first director of that historical Framingham study Dr. William Kannel concluded that multiple factors are responsible for atherosclerotic changes of the vessel and these factors together termed “*cardiovascular risk factors*”^{8,12,13}.

CVS risk factors:

Fixed: <ul style="list-style-type: none"> • Age • Male sex • Heredity (+ve F/H) • Deletion Polymorphism in ACE Gene 	Potentially changeable with treatment: <ul style="list-style-type: none"> • Hypertension • Diabetes Mellitus • Hyperlipidemia (Dyslipidaemia) • Obesity • Cigarette smoking
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Others:

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|--------------------|--|---------------|
| • IGT | • C-Reactive protein | • Soft drinks |
| • Lipoprotein (a) | • Heavy alcohol consumption | • Cocaine |
| • Lack of exercise | • Behavioral factor-Type A personality | • OCP |
| • High fibrinogen | • Homocystinemia | • Gout |

¹ Professor, Department of Medicine, Rajshahi Medical College, Rajshahi.

² Professor, Department of Medicine, Rajshahi Medical College, Rajshahi.

³ M. Phil Pharmacology (Part II), Rajshahi Medical College, Rajshahi.

⁴ Assistant Professor, Department of Cardiology, Rajshahi Medical College, Rajshahi.

Hypertension: affects about 1 billion people worldwide. The relationship between blood pressure and risk of cardiovascular events is continuous and independent of other risk factors. Blood pressure results target organ damage (TOD)³. Persons who are normotensive at age 55 have a 90% lifetime risk for developing hypertension. For persons aged 40-70 years, each increment of 20 mm of Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure doubles the risk of cardiovascular disease^{3, 7, 10}. By lowering the blood pressure TOD can be prevented. In clinical trials, antihypertensive therapy has been associated with a 20% to 25% reduction in myocardial infarction as well as a 35% to decrease in stroke and a 50% decrease in heart failure. "All patients with known ischemic heart disease should be treated to achieve blood pressure of less than 140/90 mm of Hg and it should be less than 130/80 mm of Hg in patients with diabetes or renal disease" says Joint National Committee (JNC) seventh report on prevention, detection, evaluation and treatment of high blood pressure³. They gave a clear-cut treatment protocol that includes non-pharmacological intervention and pharmacological approach. Non-pharmacological approach-the life style modification is the corner stone of management of hypertension. Not only incase of hypertension management, life style modification basically is the top charted treatment approach for all sorts of cardiovascular events.

Pre-hypertension condition requires only life style modification. Loose weight if overweight, increase aerobic physical activity (30-45 min/day), reduce salt intake, adequate dietary intake of potassium & Calcium. Adopt DASH (Dietary Approach to Stop Hypertension) eating plan. DASH is a diet low in fat and high in fruits, vegetables and low-fat dairy products that have been shown to lower blood pressure⁵².

Initial agent for treating stage 1 hypertension is Thiazide type of diuretics without compelling indication. ACE inhibitor, ARB, Beta-blocker or calcium channel blocker also can be used alone or combined. But in case of stage 2-hypertension two-drug combination is required and one of them

must be Thiazide type diuretic^{3, 7, 10, 22, 23, 24}. We may use other anti-hypertensives. In case of hypertension and compelling indication thiazide, beta-blocker, CCB, ARB and ACE Inhibitor as per the indication demands. If goal blood pressure is not achieved optimisation of dose, additional drugs and proper consultation is required. Previous major guidelines like WHO ISH, JNC sixth report and British Hypertension Society also identified diuretics especially thiazide type of respectively as initial drug for hypertension management^{3, 10, 11, 16}.

Follow-up is an important approach of hypertension management. More frequent visits for stage 2 hypertension with compelling co morbid conditions are required. Yearly electrolytes investigation should be done. If blood pressure reaches in the goal and becomes stable, follow-up visits can be done 3-6 months intervals. Frequency of follow-up visits also depends on associated complications and co morbidity. But one thing is very much important for not only the follow-up but also for diagnosis that is validated and calibrated Sphygmomanometer and proper blood pressure measurement technique. Patient should be seated quietly for 5 minutes in a chair (not on an exam table) with feet on the floor and arm supported at heart level. Do not treat patient on the basis of an isolated blood pressure reading^{3, 15, 17, 18}.

Diabetes Mellitus: is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. It is estimated that, right now more than 150 million people worldwide have diabetes, and this is expected to be double by 2010². This global pandemic principally involves type 2 diabetes. Type 2 diabetes commonly occurs in subjects who are obese and insulin-resistant, but these two factors alone insufficient to cause DM unless accompanied by impaired beta cell function. Genetic factors are important in the etiology of type-2 diabetes. The majority of cases of type-2 diabetes are multifactor in nature, with interaction of environmental and genetic factors. The nature of the genetic contribution is largely unknown²⁶. But it is evident that several genes are involved. Genes would not be sufficient to cause type 2 diabetes directly. Genome-wide searches have

identified susceptibility genes on chromosome 1 q. 12 q and 20q. But the underlying genes have not been identified. Molecular genetics has allowed the identification of certain specific and clinically identifiable forms of diabetes, which are caused by single gene defects. However these subtypes, such as maturity onset diabetes of the young (MODY) are uncommon and constitute less than 5% of all cases of diabetes²⁷.

Retrospective analysis of the birth weight of males born in England in the 1930s has demonstrated an inverse relationship between weight at birth and at 1 year, and the development of type 2 diabetes in late adulthood. Smoking during pregnancy has also been implicated. Age is an important risk factor for type 2 diabetes. In Britain over 70% of all cases of diabetes occur after the age of 50 years. Type 2 diabetes is principally a disease of the middle aged and elderly, affecting 10% of the population over the age of 65.

The insulin-secreting cells of the pancreatic islets may be unable to meet this increased demand in women genetically predisposed to develop diabetes. The term 'gestational diabetes' refers to hyperglycemia occurring for the first time during pregnancy.

Management of Diabetes: Three methods of treatment available for diabetic patients are: diet alone, oral hypoglycaemic drugs, and insulin. Approximately 50% of new cases of diabetes can be controlled adequately by diet alone 20-30% require insulin^{2,30}.

Oral Hypoglycemic Drugs: Various drugs are effective in reducing hyperglycaemia in patients with type 2 diabetes. The sulphonylureas and the biguanides have been the mainstay of treatment for many years but novel agents are now available, such as the insulin-enhancing agents- the thiazolidinediones, the alpha-glucosidase inhibitors^{2,29}.

Sulphonylureas are valuable in the treatment of non-obese patients with type 2 diabetes who fail to respond to dietary measures alone. Although sulphonylureas will lower the blood glucose concentration of obese patients with type 2 diabetes, it is often associated with hypoglycemia

and an increase in weight, which will increase insulin resistance and eventually aggravate the total disability. This leads to secondary failure to respond to the drugs, and progression to treatment with insulin. Of the second-generation sulphonylureas, gliclazide and glipizide cause few side effects, but glibenclamide is prone to induce severe hypoglycemia and should be avoided in the elderly. Newer long-acting preparations such as glimeperide and a modified-release form of gliclazide can be administered once daily with no apparent increased risk of hypoglycemia.

Metformin is the only biguanide available. The long-term benefit of metformin was shown in the United Kingdom Prospective Diabetes Study (UKPDS) but it is less widely used than the sulphonylureas because of a higher incidence of side effects. It is preferred for the obese patient. The hypoglycaemic effect of metformin is synergistic with that of the sulphonylurea drugs; the two can be combined when either alone has proved inadequate. Its use is contraindicated in patients with impaired renal or hepatic function and in those who take alcohol^{46,47}.

Acarbose or miglitol (Alpha-Glucosidase Inhibitors) is available. Both lower post-prandial blood glucose and modestly improve overall glycaemic control. They can be combined with a sulphonylurea. The main side effects are flatulence, abdominal bloating and diarrhoea. Rosiglitazone or pioglitazone (Thiazolidinediones) should be prescribed with either a sulphonylurea or metformin; they have few side-effects, although they promote weight gain and fluid retention and are contraindicated in people who have cardiac failure. Meglitinides and Amino acid Derivatives are oral prandial glucose regulators. Repaglinide directly stimulates endogenous insulin secretion and is taken immediately before food. It is less likely to cause hypoglycemia than sulphonylureas. In diabetics who are requiring increasing doses of a sulphonylurea or biguanide, either alone or in combination with each other or with thiazolidinedione, the introduction of a single dose of an intermediate-acting insulin (usually isophane), administered at bedtime, may improve

glycaemic control and delay the development of overt pancreatic beta cell failure. The exogenous insulin suppresses hepatic glucose output during the night and lowers fasting blood glucose. This treatment is ineffective in diabetic patients who have no residual endogenous insulin secretion⁴⁸.

According to United Kingdom Prospective Diabetic Study (UKPDS), 50% of newly presenting patients with type 2 diabetes already have one or more complications at diagnosis and among them the prevalence of Hypertension is 35%, Abnormal E.C.G. 18%, Stroke or TIA 1% and MI 1%. So treating this group of patients needs more attention of the clinicians in terms of reasonable approach^{49,50}.

Patients having hypertension with diabetes should be treated with a goal systolic BP of <130 and diastolic BP of <80 mm of Hg. Life style modification, not to be waited more than three months, should be advised for the patients having systolic BP ranging from 130-139 and the diastolic BP ranging from 80-89 mm of Hg. Therapeutic treatment should be advised for the patient in whom systolic BP is >140 and diastolic BP is >90 mm of Hg along with life style modification. Unless contraindicated the drug of choice for these patients is Ramipril^{12,20}.

DM with dyslipidaemia: Prevalence is 30-50% and the common pattern is elevated triglyceride & decreased HDL cholesterol. This is a strong predictor of CHD. According to NCEP, LDL-C is also a potent predictor for CVD. Dyslipidaemia with DM- Risk category based on lipid levels is, High (LDL>130, HDL>30 and triglyceride>400), Borderline (LDL>120-29, HDL>35-45 and triglyceride>200-399) and Low (LDL<100, HDL>45 and triglyceride<200)^{12,13}.

Order of priorities for treatment of diabetic dyslipidaemia is LDL lowering- 1st- Statins, 2nd- Resin or fenofibrate, HDL raising- Weight loss, physical activity, smoking cessation, Nicotinic acid or fibrates, Triglyceride lowering- 1st- Glycemic control, 2nd- fibrates, 3rd- statins and Combined hyperlipidemia- 1st- Glycaemic control

+ high-dose statins, 2nd- Glycaemic control + statins + fibrate and 3rd- Glycaemic control + statins + Nicotinic acid.

Hyperlipidaemia (Dyslipidaemia): Elevated levels of serum lipid (cholesterol and Triglycerides) are extremely common and are one of the most important risk factor. Conjugated protein composed of a lipid core and a lipid / protein coat that carry lipids through blood streams is known as lipoprotein. We know lipoproteins present in our body are: Chylomicron, Very low-density lipoprotein (VLDL), Intermediate density lipoprotein (IDL), Low density lipoprotein (LDL) and High-density lipoprotein (HDL). Other lipoproteins are Serum albumin, Z-protein and Phospholipids exchange protein (PLEP)^{5,6,35,36}.

There are two types of hyperlipidemia. Primary type is categorized as Type I, Type IIa, Type III, Type IV and Type V. Secondary type is caused by certain types of conditions such as Diabetes Mellitus, Obesity, Poor Diet, Alcohol abuse, Hypothyroidism etc. Combined hyperlipidemia is a commonly occurring form of hypercholesterolemia characterized by increased LDL and triglycerides concentrations, often accompanied by decrease HDL level. It is of two types: Familial combined hyperlipidemia and Acquired combined hyperlipidemia^{4,6,20,25}.

[LDL–low-density lipoprotein; IDL– intermediate-density lipoprotein; VLDL–very low density lipoprotein. (High-density lipoprotein (HDL) cholesterol levels are not considered in the Fredrickson classification.) (Adapted from Yeshurun *et al.*, 1995).

Pathogenesis of Atherosclerotic Plaques: Endothelial damage> Protective response results in production of cellular adhesion molecules>Monocytes and T lymphocytes attached to sticky surface of endothelial cells> Migration through arterial wall to sub endothelial space> Macrophages take up oxidized LDL–C> Lipid rich foam cells>Fatty streak and plaque^{4,5}.

Approach to cholesterol management: Third report of NCEP on Detection, Evaluation, and Treatment of High blood cholesterol in adults, (Adult treatment panel [ATP] III focus on comprehensive approach involving both therapeutic lifestyle changes (TLC) and, when appropriate drug treatment. NCEP has given emphasis on low-density lipoprotein cholesterol level. Reduction of LDL level reduces mortality 30% and major coronary events 35%^{4,6}.

Criteria for accurate lipid profile: Patient should fast for 14 hours (water & fat free liquid allowed), normal diet preceding two weeks and previous night meal should be fat free.

Dietary recommendations: Fats (Saturated fat <7%) <30% of Calories, Carbohydrate 50%-60% Protein 15%. Diet- Phytosterol, Fish oil, fiber 20-30 gm/day, cholesterol <200mg/day³⁶.

Effect of Lipid-lowering Therapies on Lipids:

Therapy	TC	LDL	HDL	TG	Patient tolerability
Bile acid sequestrants	↓ 20%	↓ 15–30%	↑ 3–5%	Neutral or up	Poor
Nicotinic acid	↓ 25%	↓ 25%	↑ 15–30%	↓ 20–50%	Poor to reasonable
Fibrates (gemfibrozil)	↓ 15%	↓ 5–15%	↑ 20%	↓ 20–50%	Good
Probucol	↓ 25%	↓ 10–15%	↓ 20–30%	Neutral	Reasonable
Statins*	↓ 15–30%	↓ 24–50%	↑ 6–12%	↓ 10–29%	Good

Obesity: may be defined as a body mass index (BMI) greater than 30. BMI = Weight in Kg / (Height in Meter)². Two types of Obesity- Android or abdominal type and Gynecoid or buttock type. Male having > 40 inches and female having >35 inches waist are considered as obese. Several causes of obesity include genetic, social, behavioral, cultural, psychological, metabolic and drugs. LEPTIN a hormone discovered in 1994 regulate adipose proliferation and modulate eating behavior. 80% of people with type-II DM are obese. It is a major factor in insulin resistance & determinant for choice of appropriate therapy^{40,41,42}.

Managing obesity is a very difficult task. 90% people who attempt to lose weight gain it all back. Reasonable goal is to lose 10% body wt over a 6 months period. Patients with BMI 27-35 should lose half kg per week. Patients with BMI above 35 should lose one kg per week.

Essential mode of therapy should be included (i) Counseling (ii) Restriction of calories (1200 -1800 Kcal) (iii) Life style modification and (iv) Physical activity (i.e. weight loss & maintenance)^{4,6}

Pharmacotherapy: Most of the drugs used in the management of obesity are not ideal.

Therapy	
Older agents	Newer agents
Dexfenfluramine Fenfluramine Phentermine (Withdrawn from market due to A/E like: Valvular heart disease etc)	Amphetamine derivatives (Not available for A/E like: Tachycardia, HTN, Addiction etc.) Sibutramine (10-20 mg/day-Appetite suppressant, Serotonergic, Thermoenergetic A/E: Tachycardia)
	Orlistat (Pancreatic lipase inhibitor Binds to lipase in the bowel Prevent fat breakdown & absorption ↓ LDL Can not be used for long time A/E: GI upset / Anal leakage common)
	Acarbose, Olestar (Beneficial effects on Metabolic syndrome NIDDM, HTN)

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35%, Abnormal E.C.G. 18%, Stroke or TIA 1% and MI 1%. So treating this group of patients needs more attention of the clinicians in terms of reasonable approach³⁶.

Smoking: Have several negative effects on the CVS. It reduces the level of “good” cholesterol (HDL) and nicotine causes BP & HR to rise. Carbon monoxide displaces O₂ in the blood, reducing the amount of available O₂ essential for the body. It is a major contributor to - CAD, Stroke and PVD. 30-40% death from CAD each year attributed to smoking. Smoker experience much greater health risk than non-smokers. Pack-a-day smokers are at twice the risk for heart attack than non-smokers and smoking two or more packs a day triple the risk. Sudden death increases more than 10 folds in men who smoke¹². Smoking cigarette that are low in nicotine and tar does not decrease the risk of heart disease. Heart attack victims are four times more likely to die if they smoke. Female smokers who use oral contraceptives are 39 times more likely to have heart attack and 22 times more likely to have a stroke. Environmental tobacco smoke or “second hand smoke” in high concentrations has been linked to CVD in nonsmokers¹³.

Behavioral factor- Type A personality: There is debate. Type A personalities are coronary prone. Sense of time pressure, chronic impatience, always in hurry and excessive hostility tends to become upset easily for funny cause.

Conclusion

Cardiovascular risk management is a very difficult task when multi component present in one person. Risk reduction involves intervention in each area in which risk is identified. Present recommendation is for proper control and management of HTN, DM, dyslipidaemia, obesity and cessation of smoking. For these non-contagious but killer diseases national as well as global economic burden is increasing. Considering the socio-economic condition in the world suggests that prevention through ‘life style modification’ is the universal ‘vaccine’ in the management of cardiovascular risk factors. Role of responsible physicians’ judgment remains paramount for motivation, empathy to the patients, selecting the drugs and adherence to the treatment for the management of this overwhelming condition.

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All correspondence to:
Quazi Tarikul Islam
 Professor of Medicine
 Rajshahi Medical College, Rajshahi