REVIEW ARTICLES

Application of Total Cardiovascular Risk Estimation in The Management of A Patient with Cardiovascular Risk

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Abstract:

Medical intervention based on the concept of total coronary risk in the asymptomatic population without cardiovascular disease (CVD) is widely advocated throughout the world.

All adults above 40 years, without history of CVD or diabetes, and who are not on treatment for blood pressure (BP) or lipids, should be considered for a comprehensive risk assessment in primary care once every five years. Our patient is an asymptomatic obese, hypertensive, dyslipidaemic individual who is also a smoker. He has a family history of premature atherosclerotic disease. His co-morbidities include mild asthma and hepatic impairment. His estimated total cardiovascular risk according to Joint British Society risk score[1] for 10 year cardiovascular event is 40% which qualifies him in the high risk category.

His estimated score according to HEART score based on the SCORE project[2] is 7% which refers to a 10-year risk mortality. According to HEARTSCORE, a score of more than 5 is considered to be at high risk. The following discussion aims to cut down his cardiovascular risk by having life-style changes and use of cardio-protective medication where appropriate.

Introduction:

Medical intervention based on the concept of total coronary risk in the asymptomatic population without cardiovascular disease (CVD) is widely advocated in the United Kingdom,[3] Europe,[4] the United States of America,[5] and globally.[6] The importance for estimating total CVD risk based on major risk factors is that: (1) the origin of CVD is multifactorial; (2) risk factors tend to cluster; and (3) co-existent risk factors tend to have multiplicative effect on CVD risk.[7] To assess the CVD risk of any individual it is important to take account of all risk factors. All adults above 40 years, without history of CVD or diabetes, and who are not on treatment for blood pressure (BP) or lipids, should be considered for a comprehensive risk assessment in primary care once every five years.

The following discussion is to explore these concepts in this patient and aims to cut down the risk by adopting a healthy lifestyle and suggest medical management by a comprehensive multi-disciplinary team approach.

Assessment of risk factors:

He is a 52 year old bus driver of .He has a calculated body mass index (BMI) of 32.35 kg/m^2 classifying him as class I obese and he is also centrally obese (waist circumference 116 cm) .He is a smoker with a 15 pack year history of smoking. His blood pressure (BP) is 155/94 which is above the normal reference range. He has got dyslipidaemia with high total cholesterol, high low density lipoproptein (LDL) (calculated LDL 3.5 mmol/l from Freidewald formula) and high triglyceride (TG). His calculated total cholesterol to HDL ratio is 5.54. His other comorbidities include mild asthma and frequent bouts of bronchitis. He also has a past history of suspected hepatic impairment. He has a family history of premature atherosclerotic disease. According to both national and European guidelines[8] this patient should be offered for a comprehensive CVD risk assessment whenever there is an opportunity by health professionals.

The above table (Table-I) summarizes his risk factors, targets to achieve according to Joint British Societies' Guidelines and action plan for him.

Table-1

(Summary of the targets, patient's risk factors, and action plan according to JBS2)

Risk Factor	Targets to achieve	Patient's risk profile	Action Plan
Smoking Habit	Stop smoking completely	Current smoker	*assessment of smoking status & nicotine dependence *counselling *nicotine replacement therapy/ drugs
Physical inactivity	Regular aerobic physical activity at least 30 minutes per day for at least 5 days per week	No regular activity of moderate intensity for 30 minutes	Encourage him to increase his physical activity gradually in work place and in leisure time to reach target
Body weight distribution	Body mass index(BMI) :< 25 kg/square meter Waist circumference:<90 cm	BMI: 32.35 (class I obese) Waist circumference: 116 cm(centrally obese)	*Increase in physical activity *calorie reducing diet
Blood Pressure	Systolic pressure < 140 mm Hg Diastolic pressure < 85 mm Hg	Systolic pressure: 155 mm Hg Diastolic pressure:94 mm Hg	*Lifestyle management *drugs
Lipids	Total cholesterol: < 4 mmol/l LDL cholesterol:<2 mmol/l Total cholesterol:[1] HDL-C ratio $\leq$ 4	Total cholesterol:6.1 mmol/l Calculated LDL cholesterol: 3.5 mmol/lTotal cholesterol: HDL ratio 5.54	*Lipid lowering diet *Exercise *drugs: statins

([1] There is no target for total cholesterol HDL ratio in JBS2)

Estimation of cardiovascular risk:

His estimated total cardiovascular risk according to Joint British Society risk score for 10 year cardiovascular event is 40% which qualifies him in the high risk category. This is illustrated in (Fig 1):

The above figure shows the estimated total cardiovascular risk of this patient for a cardiovascular event in next 10 year is 40% and the relative risk is 97% according to JBS2
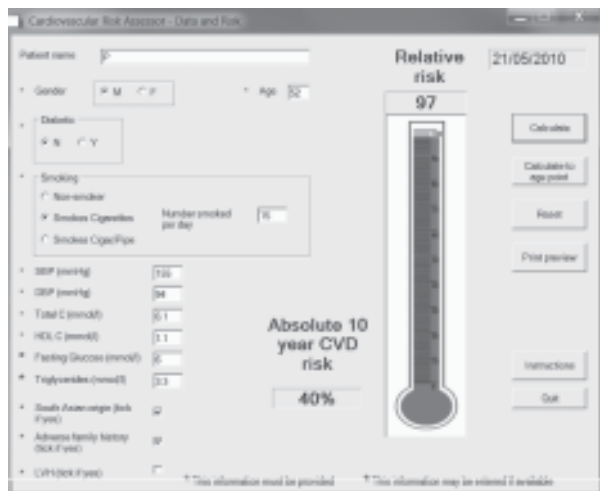

Fig.-1: *Total cardiovascular risk according to Joint British Society (JBS2, 2005)*

electronic risk assessor. The absolute risk gives the actual likelihood of an event in next 10 years whereas the relative risk can be used to encourage lifestyle change or to explain the benefits of anti-hypertensive or cholesterol lowering medication and of compliance with it.

His estimated score according to HEART score based on the SCORE project is 7% which refers to a 10-year risk mortality. According to HEARTSCORE, a score of more than 5 is considered to be at high risk.

The proportion of individual risk factors attributable to CHD deaths had been studied which found that about 6% CHD death was attributable to obesity, 12% to high blood pressure, 18% to smoking, 38% to physical inactivity and 46% to cholesterol.[9] This shows how important it is to control and improve modifiable risk factors in order to reduce total CVD risk.

Management of the individual risk factors such as smoking, unhealthy diet, physical inactivity, high BP influences total cardiovascular risk. If perfect control of a risk factor is not achieved (such as high BP), total risk can still be reduced by reducing other risk factors such as smoking or blood lipids. The electronic version of JBS2 or SCORE can be used to show the patient how the total risk decreases if individual risk is controlled. Moreover the SCORE

electronic version also demonstrates how much individual risk factor contributes to total cardiovascular risk. This may help to motivate the patient to aggressively reduce individual risk factors.

The following data and figure (2 and 3) illustrates this patients' risk score and contribution of individual risk factor to CVD mortality according to HEART-SCORE electronic version:

Examination data of this patient:

Patient name	: x	
Age	52 years DOB: (7/1957)	
Sex	Male	
Risk factors	Examination	Treatment goals
Systolic blood pressure	154	140
Cholesterol	6.1 mmol/L	5 mmol/L
Smoker	Yes	No
Your total CVD risk*	7%	2%

* Total CVD risk refers to the 10-year risk mortality

Actual Total CVD Risk Level
The total cardiovascular disease risk level (left bar below) shows the percentage risk of having a fatal cardiovascular event, such as a stroke or heart attack. Based on examination results, his total CVD risk is 7%.

However, by becoming aware of his risk factors and taking a few preventive actions, he can reach the treatment goals and reduce his risk to 2% as shown by the treatment goal level (right bar below).
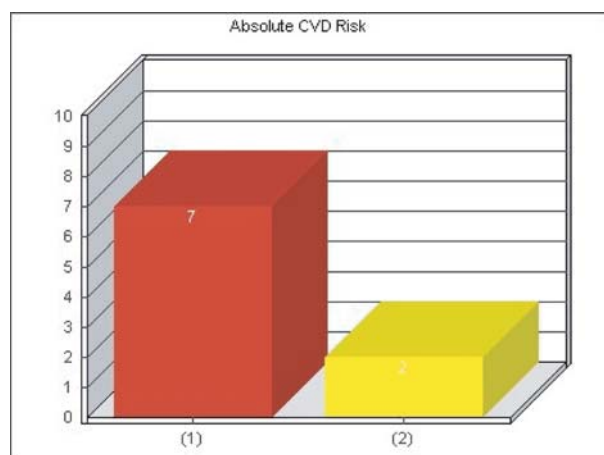
(1) His current risk is 7% (2) His risk if he reaches his treatment goals will approach 2%

Fig 2: *The above figure shows this patient's total CVD risk and risk reduction if he reaches the treatment goal.*

At present, his risk of dying from a heart attack or a stroke within the next ten years is increased. He can reduce this risk further by becoming aware of his risk factors and by changing his lifestyle.

Distribution of Modifiable Risk Factors
Cardiovascular disease is generally due to a combination of several risk factors. The more risk factors he has, the greater the chance of having a heart attack or stroke. The pie chart below shows the distribution of his modifiable risk factors and the impact they have on his total CVD risk level.
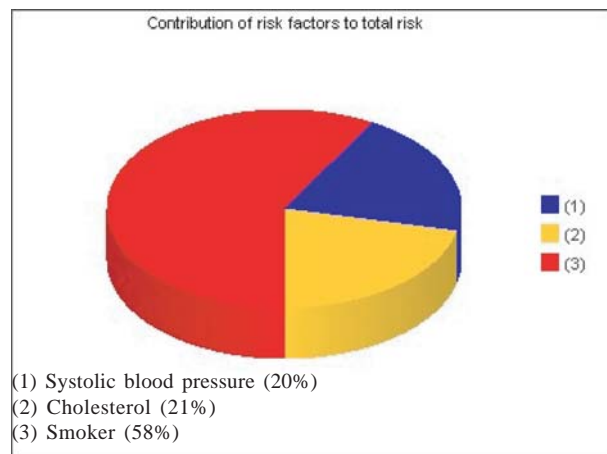

(1) Systolic blood pressure (20%)
(2) Cholesterol (21%)
(3) Smoker (58%)

Fig.-3: *The above pie chart shows contribution of individual risk factors to total CVD risk.*

Presence of metabolic syndrome:
A diagnosis of metabolic syndrome can be made in this patient because he has increased waist circumference, elevated TG, and elevated BP. The clustering of these factors has been termed the metabolic syndrome.[10] People with metabolic syndrome are at higher risk of CVD because this syndrome is based on several interrelated CVD risk factors.[11]

Lifestyle intervention:
As part of lifestyle intervention he needs to discontinue smoking, make healthier food choices, increase aerobic physical activity and achieve optimal weight. Involvement of his family such as his wife may be helpful. The patient should be informed about the benefits of reducing weight, quitting smoking, participating in regular aerobic exercise and making healthier eating habits. Once he understands this, it can be used to gain commitment from the patient to lifestyle change. The progress can be monitored through follow-up contacts. The involvement of other health-care staff wherever possible is the key to success.

Management of individual risk factors:

Smoking cessation

All smokers like him should be professionally encouraged to permanently stop smoking. Detailed smoking history including his degree of addiction and his readiness to cease smoking should be assessed.[12] The Fagerstrom Test for Nicotine Dependence (FTND) provides a validated tool which can be used to measure his physical dependence on smoking. He might be physically dependent on smoking as he has a 15 pack year of smoking history. Pharmacologic treatment for smoking cessation like bupropion & varenicline is not available in our country. Behavioural support includes setting up a firm quit date with him, guiding and informing him of the support services such as attending a smoking cessation clinic, ascertaining his motivation to quit smoking by using scaling questions, agreeing with him achievable goals and ensuring he understands what the medication can and cannot do and use it properly. Smoking is the single most important preventable cause of disease and early death.[13] If asymptomatic smokers quit smoking it takes up to 10 years to reach the same level of CVD risk of those who have never smoked.[14,15] An arrangement for the schedule of follow-up visits is helpful.

Diet:

Higher risk persons like him should be advised about food choices that are associated with lower CVD risk. As he is centrally obese energy intake should be adjusted to lose weight and he should be referred to a dietician. He should be encouraged to increase fresh fruit and vegetables to at least 5 portions per day along with wholegrain cereals and bread, oily fish (at least 2 servings per week), lean meat and low fat dairy products. The aim is to replace saturated fats to less than 10% of total fat intake with monounsaturated and poly unsaturated fats from vegetable and marine sources to reduce total fat to less than 30% of energy. This is also known as Mediterranean diet which is associated with a decreased risk of CVD. The intake of dietary cholesterol should be restricted to less than 300 mg/day. By adhering to a low cholesterol diet, up to 15% of total cholesterol can be reduced. In cohort studies, the positive relationship between fat intake and CVDs was related to their saturated fatty acid content.[16] A meta-analysis of randomised controlled trials (RCT) of reducing saturated fat intake (using monounsaturated or polyunsaturated fats as a replacement) with at 2 years follow-up resulted in a significant reduction in CVD events by 24%.[17] Plant stenols and sterols reduce LDL cholesterol (an average of 0.54 mmol/l for 2 gram plant stenol or sterol/day).[18]

Reduction of weight:

Restriction of total calorie intake and regular physical exercise are the cornerstones of weight control. Replacing high-calorie food and reduction of total intake is a realistic option. Most people begin to gain weight a few months after their initial treatment. Sustained personal and family motivation and long term professional support is required for a successful weight reduction.

He currently weighs 79 kg. Benefits associated with a 10kg weight loss in a 100kg subject is mentioned in Table 3[19]:

Table-III

Benefits of a 10 kg weight loss in a 100 kg subject

Mortality	20-25% decrease in premature mortality
BP	10 mm decrease in SBP20 mm decrease in DBP
Lipids	10% decrease in total cholesterol15% decrease in LDL cholesterol8% increase in HDL cholesterol30% decrease in TG
Diabetes	Reduces risk of type 2 diabetes by 50%30-50% decrease in elevated blood glucose15% decrease in HbA1c

This patient may be recommended drug therapy such as orlistat according to current guidelines with regular exercise and diet restriction. In a meta-analysis, orlistat reduced weight by 2.7 kg (95% CI 2.3 to 3.1 kg).[20] In another trial the progression to diabetes was reduced by 39% compared to placebo by lifestyle change supplemented with orlistat. The risk of CVD proportionately increases with the increase in BMI.[21] Increased CVD risk is also related to the distribution of visceral fat.[22] Weight reduction leads to lower BP, LDL, TG and higher HDL cholesterol, and an improvement in other elements of the metabolic syndrome such as hyperinsulinaemia and hyper-glycaemia.[23]

Physical Activity:

Positive health benefits have been noticed with almost any increase in activity. He should be referred to a physical activity specialist ideally for professional assessment. He can increase his leisure-time activity by engaging in some more vigorous activity such as brisk walking which is an important determinant of long-term weight maintenance after initial weight loss.[24] As he gradually increases his activity up to a minimum of 30 minutes of moderately vigorous exercise like fast walking in most days of the week will reduce risk and increase fitness. Exercise with family or friend tends to improve motivation. Continued encouragement and support from the physician may help

in the long term. Regular physical activity is protective through a wide variety of beneficial effects. According to WHO data, up to 24% of CHD is due to levels of physical activity below 2.5 hours of moderate intensity activity per week. It is estimated that about 36% of deaths from CHD in men and 38% in women are due to lack of physical activity.[25]

Rationale for drugs:

The choice of risk assessment method will influence on the use of drug therapies in asymptomatic people[26]. For asymptomatic individuals without CVD the total CVD risk threshold defined in guidelines for professional lifestyle intervention and appropriate drug therapies is more than 20% over 10 years, which is equivalent to a coronary heart disease (CHD) risk of more than 15% over the same period.. According to HEARTSCORE the risk threshold for treatment is therefore defined as fatal CVD of more than 5% over the next 10 years at current age. This is equivalent to a CVD risk of more than 20% based on Framingham.

Control of high blood pressure:

As his BP is above the normal range, repeat measurements (2 measurements at each visit) over 4 visits to determine BP thresholds for treatment, including an assessment of target organ damage should be done. If his BP is persistently over 140/90 mm Hg, he should receive lifestyle advice to help reduce his BP and CVD risk.[27] The aim is to reduce his BP to less than 140/85 mm Hg. Lifestyle recommendations include weight reduction, reduction of salt intake to less than 100 mmol/l daily by avoiding table salt and salt in cooking and by choosing fresh or frozen unsalted foods, restriction of alcohol consumption to less than 14 units/week (for females where applicable), regular physical activity, quitting smoking and dietary changes for dyslipidaemia.

The DASH study showed that a diet high in fruit and vegetable and low-fat diary products, and low in saturated fat and cholesterol, produced a reduction of SBP by 11.4 mm Hg & DBP by 5.5 mm Hg.[28] Reduced salt intake by patients with high BP leads to a reduction of SBP by 4.8 mm Hg and DBP by 2.5 mm Hg.[29] Reduction of alcohol consumption can reduce SBP by 3.1 mm Hg and DBP by 2.04 mm Hg. [30]

If BP is still more than 140/90 mm Hg despite lifestyle changes he should receive drug therapy. As his total CVD risk is > 20% drug treatment is justified. Presence of target organ damage or diabetes also justifies drug treatment in patients with high BP. The British Hypertension Society (BHS) ACD algorithm can be followed for drug treatment.

He should be started initially with a angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). If BP is still e" 140/85, a calcium channel blocker (CCB) may be added later on to reach the target. Common problem with ACEI is dry cough which is much less in ARBs. CCB like amlodipine is well tolerated but can cause pedal oedema. Use of diltiazem may further reduce heart rate as this patient has a resting heart rate of 62/minute. Lifestyle advice should continue even when drug therapy is initiated. The risk of CVD doubles for every 10 mm increase in diastolic BP or every 20 mm Hg increase in systolic BP[31]. A reduction in systolic BP by an average of 12 mm Hg or diastolic BP of 6 mm Hg reduces stroke by 40% and CHD by 20%.[32]

A meta-analysis of 147 RCTs showed that proportional reduction in CHD events and stroke for a given reduction in BP, an approximate halving of risk for each 10 mm Hg diastolic reduction, is the same in people with and without a history of vascular disease and in people without high BP as well as in those with high BP. There is benefit in lowering BP in anyone at sufficient cardiovascular risk whatever their BP.[33]

Lipid management:

The aim of lipid management should be total cholesterol of less than 4 mmol/l or a 25% reduction and LDL cholesterol of less than 2 mmol/l or a 30% reduction. HDL cholesterol and TG values should also be considered in overall lipid management. The risk of CVD rises proportionately with the rise in TG when HDL values are low. He should receive intensive lifestyle advice to modify his lipoproteins favourably which will reduce CVD risk. His lipids should be monitored regularly, and not less than once per year. In addition to a lipid lowering diet treatment with statin therapy is justified as he has > 20% total CVD risk. Presence of atherosclerotic disease and diabetes also justifies statin therapy. Over a wide range of cholesterol concentrations, there is a strong and graded positive association in men and women between total as well as LDL-cholesterol and the risk of CVD.[34] In contrast to LDL-cholesterol, the cardioprotective effects of HDL-cholesterol have been linked to reverse cholesterol transport, positive effects on endothelial cells, and to antioxidant activity.[35] Statin trials in asymptomatic individuals at risk of CVD have shown significant reductions in coronary events and coronary mortality.[36] The reduction of cholesterol by diet, drugs or other means decreases CVD risk.[37]

A meta-analysis involving 10 trials investigated whether statins reduce all-cause mortality and major coronary and cerebrovascular events in people without established CVD

but with cardiovascular risk factors. The results demonstrated statins significantly reduced all-cause mortality (odds ratio [OR] 0.88, 95% confidence interval [CI] 0.81 to 0.96), major coronary events (OR 0.70, 95% CI 0.61 to 0.81), and major cerebrovascular events (OR 0.81, 95% CI 0.71 to 0.93).[38]

His fasting glucose is 6 mmol/l. In all high risk people the optimal fasting glucose should be less than 6 mmol/l. He should therefore receive lifestyle advice in the form of diet, weight reduction and regular exercise. Orlistat is helpful as he is obese and studies show that it reduces progression to diabetes.[39]

Other comorbidities:

He has a mild asthma and frequent bouts of bronchitis. He should be emphasized that continuing smoking may further aggravate his asthma and bronchitis. This information may motivate him to quit smoking.

He has a past history of suspected hepatic impairment. This should be further explored in view of the fact that he might me prescribed statin for control of lipids. Therefore active hepatic disease should be ruled out. His liver function tests should include hepatic enzymes such as transaminase (ALT), gamma glutamyl transferase (GGT), serum total protein, albumin globulin ratio, prothrombin time, hepatic ultrasound and virology screen. Current recommendations include at least baseline hepatic enzymes before starting statin therapy. A 3 fold rise in ALT from upper normal limit suggests stopping statin therapy.

Suggested further investigations related to cardio-vascular risk:
People like him who are found to be at high total CVD risk should be asked about any new symptoms related to CVD including family history. In subsequent visits further investigations may be offered for example an oral glucose tolerance test (OGTT) if fasting blood glucose is high ($\geq$ 6.1 and $\leq$ 7mmol/l), urine for microalbuminuria, serum creatinine, electrocardiography (ECG), echocardiography etc for the subsequent and comprehensive management of cardiovascular risk.

Conclusion:
Risk factor modifications have been shown to reduce CVD mortality and morbidity, particularly in high risk individuals. Total CVD risk in asymptomatic individuals based on major risk factors can be estimated by JBS2 risk score, QRISK assessment tool or by HEARTSCORE. Aggressive control of these risk factors thereby minimising the risk of future

events is central to CVD prevention. This can be achieved by intensive and professional life style intervention and appropriate treatment where it is necessary.

In summary, his non-modifiable risk factors include ethnicity, gender, age and positive family history of premature CVD. His modifiable risk factors include high blood pressure, dyslipidaemia, smoking, physical activity not reaching the target and central obesity. His co-morbid states include mild asthma, frequent bouts of bronchitis and suspected hepatic impairment all of which should be considered during drug therapy.

The modifiable risk factors will be managed by a combination of behavioural approach, lifestyle changes and drug therapy. Drug treatment for hypertension is necessary when total CVD risk exceeds 20% as in this case or presence of target organ damage or diabetes. Similarly drug treatment for lipids is justified when total CVD risk exceeds 20% as in this case or presence of atherosclerotic disease and diabetes.

By modifying risk factors we aim to reduce CVD mortality and morbidity particularly in high risk individuals.

References:

1. JBS 2. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart,* 91 (Supplement V), 2005. v13.

2. Conroy, R. M., Pyorala, K., Fitzgerald A.P. et al. Prediction of 10-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J,* 2003; 24: 987-1003.

3. Wood, D. A., Darrington, P., Poulter, N. et, al. Joint British Recommendations on prevention of coronary heart disease in clinical practice. *Heart,* 1998; 80: S1-29.

4. DeBacker, G., Ambrosioni, E., Borch-Johnsen, K. et, al. European guidelines on cardiovascular disease prevention in clinical practice.Third Joint Task Force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Eur J Cardiovasc Prevention Rehabilitation,* 2003; 10 ((Suppl 1): S2-78.

5. NCEP. National Cholesterol Education Program.Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high cholesterol in adults (adult treatment panel III). *JAMA,* 2001: 285: 2486-97.

6. Smith, S. C., Jackson, R., Pearson, T. et al. Principles for national and regional guidelines on cardiovascular disease prevention. A scientific statement from World Heart and Stroke Forum. *Circulation,* 2004; 109(31): 12-21.

7. Anderson, J. W. & Kanz, E. C. Obesity and disease management: effect of weight loss on co-morbid conditions. *Obes Res,* 9 (suppl 4), 2001; 326S-34S.

8. www.escardio.org accessed on 10-03-2010

9. Britton, A. & McPherson, K. Potency of Coronary Heart Disease Risk Factors.British Heart Foundation. National Heart Forum 2000.

10. Grundy, S. M. Obesity, metabolic syndrome, and cardiovascular disease. *J Clin Endocrinol Metab,* 2004; 89: 2595-2600.

11. Reaven, G. M. Banting lecture 1998. Role of insulin resistance in human disease. *Diabetes,* 1998; 37: 1595-607.

12. Balfour, D., Benowitz, N., Fagerstrom, K. et al. Diagnosis and treatment of nicotine dependence with emphasis on nicotine replacement therapy. A status report. *Eur Heart J,* 2000; 21: 438-45.

13. Mackay, J. & Mensah, G. *WHO Atlas of Heart Disease and Stroke.* Geneva, Report number: Nonserial WHO Publication. 2004.

14. Dobson, A. J., Alexander, H. M., Heller, R. F. et al. How soon after quitting smoking does risk of heart attack decline? *J Clin Epidemiol,* 1991; 44: 1247-53.

15. Rosenberg, L., Kaufman, D. W., Helmrich, S. P. et al. The risk of myocardial infarction after quitting smoking in men after 55 years of age. *N Engl J Med,* 1985; 313: 1512-14.

16. Kushi, L. H., Lew, R. A., Stare, F. J. et al. Diet and 20-year mortality from coronary heart disease. The Ireland-Boston Diet-Heart Study. *N Engl J Med,* 1985; 312: 811-18.

17. Hooper, L., Summerbell, C. D., Higgins, J. P. et al. Dietary fat intake and prevention of cardiovascular disease: systematic review. *BMJ,* 2001; 322: 757-63.

18. Bucher, H. C., Hengstler, P., Schindler, C. & Meier, G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med,* 2002; 112: 682-92.

19. Jennings, C. S., Mead, A. C., Jones, J. L. et al. Preventive Cardiology: A Practical Manual, First edition, New York, Oxford University Press, 2009; p 173.

20. Padwal, R., Li, S. K. & Lau, D. C. W. Long term pharmacotherapy for overweight and obesity: a systemic review and meta-analysis of randomized controlled trials. *Int J Obesity,* 2003; 27: 1437-46.

21. Calle, E. E., Thun, M. J., Petrelli, J. M. et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New Engl J Med,* 1999; 341: 1097-105.

22. Despres, J. P. Health consequences of visceral obesity. *Ann Med,* 2001; 33: 534-41.

23. Anderson, K. M., Odell, P. M., Wilson, P. W. F. et al. Cardiovascular disease risk profiles. *Am Heart J,* 1990; 121: 293-8.

24. Baak, M. A. V., Mil, E. V., Astrup, A. V. et al. Leisure-time activity is an important determinant of long-term weight maintenance after weight loss in the Sibutramine Trial on Obesity Reduction and Maintenance (STORM Trial). *Am J Clin Nutr,* 2003; 78: 209-14.

25. WHO. Cardiovascular Disease. Geneva: WHO. Available from: http://www.who.int/cardiovascular.diseases/resources/atlas/en/ 2006.

26. Durrington, P. N., Prais, H., Bhatnagar, D. et al. (1999) Indications for cholesterol-lowering medication: comparison of risk assessment methods. *Lancet,* 1999; 353: 278-81.

27. Williams, B., Paulter, N. R., Brown, M. J. et al. Guidelines for management of hypertension: report of fourth working party of the British Hypertension Society, 2004-BHS IV. *J Human Hypertens,* 2004; 18: 139-85.

28. Appel, L. J., Moore, T. J., Obarzanek, E. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *New England Journal of Medicine,* 1997; 336(16): 1117-24.

29. Cutler, J. A., Follmann, D., and Allender, P.S. Randomized trials of sodium reduction: an overview. *American Journal of Clinical Nutrition*, 1997; 65(2 Suppl): 6435-515.

30. Xin,X., He, J., Frontini, M. G. et al. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*, 2001; 38(5): 1112-17.

31. Lewington, S., Clarke, R., Qizibash, N., Peto, R. & Collins, R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data fppr one million adults in 61 prospective studies. *Lancet,* 2002; 360: 1903-913.

32. Blood Pressure Lowering Treatment Trialist's Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospective-designed overviews of randomized trials. *Lancet,* 2003; 362: 1527-45.

33. Law, M.R., Morris, K& Wald, N. J. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectation from prospective epidemiological studies. BMJ, 2009; 338, b2376doi: 10, 1136/bmj.b2376.

34. Sharrett, A.R., Ballantyne, C.M., Coady, S. A. et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-1 and B, and HDL density subfractions: The Atheroscerosis Risk in Communities (ARIC) Study. *Circulation,* 2001; 104: 1108-113.

35. Assmann, G. & Gotto, A. M., Jr. HDL cholesterol and protective factors in atherosclerosis. *Circulation,* 2004; 109, 1118-114.

36. Shepherd, J., Cobbe, S. M., Ford, I. et, al. Prevention of coronary heart disease with pravastatin in men with hypercholesterlemia. West of Scotland coronary prevention study group. *N Engl J Med,* 1995; 333: 1301-7.

37. Bucher, H. C., Griffith, L. E. & Guyatt, G. H. Systematic review on the risk and benefit of different cholesterol-lowering interventions. *Arterioscler Thromb Vasc Biol,* 1999; 19: 187-95.

38. Brugts, J. J., Yetgin, T., Hoeks, S. E. et al The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ*, 2009; 338: b2376 doi:10,1136/bmj.b2376

39. Torgerson, J. S., Hauptman, J., Boldrin, M. N. et, al. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese people. *Diabetes Care,* 2004; 27: (155), 61.