AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Review on Significance of Risk Assessment In Cardiovascular Diseases

D.Syam Prakash[1], V.Leela Lavanya[1], P.SAI Tulasi[1], V.Satyanarayana[2*]

1. *V Pharm.D Students, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.*
2. *Assistant. Professor, Department of Pharmacy Practice, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.*

ABSTRACT

Cardiovascular diseases(CVD) account for nearly one third of all deaths world wide. Consequently the prevention of risk factors for CVD is public health priority in recent times. The available rehabilitation and preventive measures include lifestyle modification, treatment with drug and intervention procedures. The appropriate application of risk assessment should result in a better quality of life for people with cardiovascular diseases and improve cost effectiveness of healthcare. The success of these measures depends laregely on the skills of patients in the daily management of their condition. The present study reveals that risk assessment can answer many questions in best therapeutic outcomes.

Keywords: Cardiovascular disease, Risk assessment, Therapeutic outcome, Quality of life, Cost effectiveness

*Corresponding Author Email:veeragandamsatya@gmail.com
Received 14June2016, Accepted20 July2016

Please cite this article as:Satyanarayana V *et al.*,A Review on Significance of Risk Assessment In Cardiovascular Diseases. American Journal of PharmTech Research 2016.

INTRODUCTION

Cardiovascular disease (CVD) is a general term that describes a disease of the heart or blood vessels.

Blood flow to the heart, brain or body can be reduced as the result of a blood clot (thrombosis), or by a build-up of fatty deposits inside an artery that cause the artery to harden and narrow (atherosclerosis)[1].

EPIDEMIOLOGY:

- Cardiovascular diseases (CVDs) are the leading cause of death in men and women.
- Cardiovascular disease (CVD) is the leading cause of death in India, contributing to nearly one-third of all deaths. Coronary heart disease (CHD) deaths, a major contributor to CVD deaths in India, rose from 1.17million in 1990 to 1.59 million in 2000 and are further projected to rise to 2.03 million in 2010.
- Risk stratification and identification of individuals with a high risk for CHD who could potentially benefit from intensive primary prevention efforts are critically important in reducing the burden of CVD in India [2].
- CVDs are the number 1 cause of death globally: more people die annually from CVDs than from any other cause.
- An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke.
- Over three quarters of CVD deaths take place in low- and middle-income countries.
- Out of the 16 million deaths under the age of 70 due to non-communicable diseases, 82% are in low and middle income countries and 37% are caused by CVDs.
- Most cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies.
- People with cardiovascular disease or who are at high cardiovascular risk (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidaemia or already established disease) need early detection and management using counselling and medicines, as appropriate [3].

TYPES OF CVD:

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels and they include:

- Coronary heart disease – disease of the blood vessels supplying the heart muscle.
- Cerebrovascular disease – disease of the blood vessels supplying the brain.
- Peripheral arterial disease – disease of blood vessels supplying the arms and legs.
- Rheumatic heart disease – damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria.
- Congenital heart disease – malformations of heart structure existing at birth.
- Deep vein thrombosis and pulmonary embolism – blood clots in the leg veins, which can dislodge and move to the heart and lungs.

Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots. The cause of heart attacks and strokes are usually the presence of a combination of risk factors, such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, hypertension, diabetes and hyperlipidaemia.[3].

RISK FACTORS OF CVD (Table 1) :

Independent /established major	**Dependent/emerging novel**
Non modifiable • **Age** • **Gender** • **Family history** • **established** Modifiable risk: • **Diabetes mellitus** • **Hypertension** • **Hypocholesteremia** • **Sedentary life style** • **Low HDL** • **Cigarette smoking** • **Obesity**	▪ ↑Homocysteine ▪ Lp ▪ Small dense HDL cholesterol ▪ Other lipid disorders ▪ Abnormalities in blood coagulation - ↑plasma fibrinogen - ↑Coagulation factors V VII VIII - Platelet abnormalities ▪ Inflammatory markers - Interlukines - C- reactive protien ▪ Short stature ▪ Impaired glucose tolerance ▪ Increased oxidative stress ▪ Personality type ▪ Sinus tachycardia ▪ LVH ▪ Air Pollution ↑ Serum Creatinine

(Table 2)[4] :

Risk factor	Measurement
Blood pressure	Absolute risk calculators have been developed using clinic BP measurements, therefore, if using ambulatory BP readings for risk assessment, clinicians should convert to the clinic equivalent using the appropriate tables (see National Heart Foundation and High Blood Pressure Research Council of Australia consensus statement 2012). For clinic BP measurement, the average of two seated BP measurements over two separate occasions should be used to calculate risk. The most recently recorded pre-treatment value can be adopted for individuals taking antihypertensive medication. Ambulatory BP measurement is a better predictor of outcomes than clinic BP measurements and therefore should be used to monitor BP lowering therapy.
Serum lipids	A fasting lipid profile (TC, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], non-high-density lipoprotein cholesterol [non HDL-C], TC: HDL ratio and triglycerides) should be taken. A single TC: HDL ratio is used to calculate CVD risk. When a fasting sample is not possible, a non-fasting TC:HDL ratio may be used for an initial screening assessment of CVD risk, however treatment decisions should be made on the basis of fasting lipid levels.
Plasma glucose	In order to screen for diabetes, an assessment of fasting plasma glucose is recommended. A value of≤ 5.4 mmol/L indicates a normal level. A result of 5.5–6.0 mmol/L may be normal but some people will show diabetes or impaired glucose tolerance in an oral glucose tolerance test (OGTT). A value of≥ 6.1 mmol/L but ≤ 6.9 mmol/L is diagnostic of impaired fasting glucose and requires an OGTT to confirm diabetes or impaired glucose tolerance. A value of≥ 7.0 mmol/L on two separate occasions is diagnostic of diabetes and does not require an OGTT. When a fasting sample is not possible non-fasting glucose can be measured with further testing required if the result is ≥5.5 mmol/L. HbA1c can be used to diagnose diabetes with a level of≥6.5% being diagnostic
Waist circumference and BMI	A BMI <25 kg/m2 is desirable. Individuals with a BMI ≥25 kg/m2 are classified as overweight and those with a BMI ≥30 kg/m2 are obese and at increased risk of diabetes, CHD and stroke compared with individuals with normal BMI (< 25 kg/m2).Waist circumference, as a measure of central obesity, is a better predictor of CVD risk than BMI. A waist circumference of ≥94 cm in men (≥90 cm in Asian men) and ≥80 cm in women (≥80 cm in Asian women) is suggestive of central obesity.
Left ventricular hypertrophy (LVH) (If assessed	Echocardiography, if available, should be the test of choice to assess for LVH as it is more sensitive than electrocardiography. In the absence of echocardiography, electrocardiograms can be used.
Renal function	Renal function should be estimated from GFR. An eGFR <60 ml/min/1.73m2 is indicative of stage 3 CKD. Proteinuria is defined as urinary albumin: creatinine ratio (UACR) > 35 mg/mmol in females and >25 mg/mmol in males. Persistent proteinuria is defined as 2 positive measurements, 3 months apart. The preferred method for assessment of proteinuria in both diabetic and non-diabetic patients is UACR in a first void spot specimen. Where a first void specimen is not possible or practical, a random spot urine specimen for

	UACR is acceptable. A positive UACR test should be repeated to confirm persistence of albuminuria. CKD is present if two out of three tests (including the initial test) are positive. If the first positive UACR is a random spot (as it may be for opportunistic testing), then repeat test results should ideally be first morning void specimens.
Smoking status	For the purposes of CVD risk assessment, a non-smoker is defined as someone who has never smoked or has given up smoking and has not smoked for ≥12 months.

MANAGEMENT:

Effect of lifestyle and dietary factors on CVD outcomes

(Table 3) :

Reference	Study details	Intervention	Results
Brunner *et al* (2007)[6]	Good quality SR (n=38 RCTs); 17,871 healthy Adults. Median follow-up 10 Months	Dietary advice Vs no advice or Minimal advice	↓TC 0.16 mmol/l, ↓ LDL-c 0.18 mmol/l, ↓SBP 2.07 mmhg / DBP 1.15 mmhg After 3-24 months. Mean HDL-c levels and Triglyceride levels unchanged.
Dickinson *et al* (2006)[7]	Good quality SR (n=105 RCTs); 6,805 adults with BP ≥140/85 mmhg. At Least 8 weeks follow-up.	Lifestyle Interventions vs Control	Improved diet ↓SBP 5.0 mmhg; ↑aerobic Exercise ↓SBP 4.6 mmhg; ↓ alcohol ↓SBP 3.8 mmhg; sodium restriction ↓SBP 3.6 Mmhg; and fish oil supplements ↓2.3 Mmhg.
Dauchet *et al* (2005)[8]	Good quality SR (n=7 Prospective cohort studies); 232,049 participants; 90,513 men, 141,536 Women.	Vegetables and Fruit	↓ risk of stroke (RR 0.89, 95% CI 0.85-0.93) For each additional portion per day of fruit. ↓ Risk of stroke (RR 0.95, 95% CI 0.92-0.97) For additional fruit and vegetables per day. Linear relationship between fruit or fruit and Vegetables and stroke.
Dauchet *et al* (2006)[9]	Good quality SR (n=9 Prospective cohort studies); 221,080; 91,379 men, 129,701 women.	Vegetables and Fruit	For each additional portion per day of Vegetable and fruit ↓ risk CHD (RR 0.96, 95% CI 0.93-0.99). For each additional Portion per day of fruit

			intake ↓ risk of CHD (0.93, 95% CI 0.89-0.96).

Effect of physical activity on CVD outcomes

(Table 4) :

Reference	Study details	Intervention	Results
Hamer *et al* (2008)[10]	Good quality SR (n=18 Prospective cohort studies). 459,833 participants free from CVD at baseline.	Walking	For highest vs lowest walking category: ↓CVD events (HR 0.69, 95% CI 0.61-0.77) ↓all-cause mortality (HR 0.68, 95% CI 0.59-0.78). Walking pace was a stronger Independent predictor of overall risk compared With walking volume (48% vs 26% risk Reductions, respectively).
Lollgen *et al* (2009)[11]	Good quality SR (n=38 Prospective cohort studies) Primary prevention. Study Duration > four years. >271,000 participants.	Physical activity	All-cause mortality. Highly vs mildly active: Men (RR = 0.78, 95% CI 0.72-0.84); Women (RR 0.69, 95% CI 0.53-0.90. There is a dose response Curve from sedentary subjects to Those with mild and moderate exercise. This Association was similar for sex and age.
Nocon *et al* (2008)[12]	Fair quality SR (n=33 Cohort studies). 883,372 Participants. Follow-up from 4 to >20 years.	Physical activity	↓CV mortality by 35% and ↓all-cause Mortality by 33% in both men and women.
Orozco *et al* (2008)[13]	Good quality SR (n=8 Rcts; 10 interventions) 5,095 participants at risk Of diabetes. Study duration Ranged from one to six Years.	Exercise or Exercise and diet	Exercise and diet interventions had a modest Effect on blood lipids, and improved SBP and DBP by 4 mmhg, (95% CI -5 to -2) and 2 mmhg, (95% CI -3 to -1), respectively. Exercise alone or diet alone did not Demonstrate these effects.

General lifestyle advice

(Table 5) **Error! Reference source not found.**

:

Lifestyle factor	Advice
Diet	Consume a varied diet rich in vegetables, fruits, wholegrain cereals, lean meat, poultry, fish, eggs, nuts and seeds, legumes and beans, and low-fat dairy products
Fats	Limit foods containing saturated and trans fats
Salt	Limit salt to <6g/day (approximately 2300 mg sodium)
Alcohol	Limit alcohol intake to ≤2 standard drinks per day
Physical activity	At least 30 minutes physical activity on most or preferably every day of the week
Weight	Limit energy intake to maintain a healthy weight. Ideal weight should be BMI <25 kg/m2 and waist circumference <94 cm in men (<90 cm in Asian men) or <80 cm in women (including Asian women)
Smoking	Stop smoking using counselling, and if required nicotine replacement therapy or other medication

Effect of blood pressure-lowering on CVD outcomes

(Table 6) :

Reference	Study details	Intervention	Results
BP Lowering Treatment Trialists' Collaboration; Turnbull et al (2008)[14]	Good quality SR (n=31 RCTs); 190,606 participants. Compared age groups <65 and above 65. Mixed primary and secondary prevention.	Comparison of BP lowering regimens against placebo or less intensive control	No difference in reductions in major CV events between age groups for any comparison. For each ↓5mmHg SBP, risk of CVD events ↓11.9% (5.3-18%) for those aged <65 and ↓9.1% (3.6-14.3%) for those aged ≥65
Wang *et* al (2005)[16]	Good quality SR (n=10 rcts). 12,903 young (30-49 yrs Old) from 3 trials; 14,324 old (60-79 yrs) and 1209 very old (≥=80 yrs old) from 8 trials. Limited to trials with available Individual data. Combined Primary and secondary trials.	All BP lowering medications vs placebo or no treatment	↓BP in young (8.3/4.6 mmHg), old (10.7/4.2 mmHg) and very old (9.4/3.2 mmHg). ↓17% all-cause mortality (p=0.003) and ↓21% CVD morality (p=0.004) in those 60-79 but not in the younger or older groups. No difference in CVD events for different ages but ↓absolute benefit with increasing age. Effects related to ↓SBP rather than DBP.

Effect of lipid-lowering on CVD outcomes

(Table 7) :

Reference	Study details	Intervention	Results
Allerman *et al* (2006)[17]	Good quality SR (8 RCTs). 12,249 participants with type 2 diabetes +/- CVD (78% were primary prevention)	Fibrates vs placebo	□ CHD events (RR 0.84, 95% CI 0.74–0.96). No effect on death due to CHD, MI or stroke. No difference between primary and secondary prevention trials.
Amarenco *et al* (2009)[18]	Good quality SR (n=26 RCTs). 165,792 participants. Mix of primary and secondary prevention.	Statins vs placebo	Each 1.0 mmol/L decrease in LDL-C equates to a reduction in relative risk for stroke of 21.1% (95% CI 6.3–33.5, p=0.009).

Effect of aspirin on CVD outcomes

(Table 8) :

Reference	Study details	Intervention	Results
Berger *et al* (2006)[19]	Good quality SR (n=6 RCTs –same as above). 51,342 women and 44,114 men.	Aspirin vs placebo	CV events (OR 0.88, 95% CI, 0.79 to 0.99). No effect on MI or CV mortality. In men, 32% ↓MI (OR 0.68, 95% CI 0.54–0.86). In women, 24% ↓ischaemic stroke (OR 0.76,; 95% CI 0.63–0.93). Aspirin ↑risk of bleeding in both men and women.
Calvin *et al* (2009)[20]	Good quality SR (n=8 RCTs). 89,392 participants without CVD; 11,634 with Diabetes.	Aspirin vs placebo	Overall mortality (OR 0.93, 95% CI 0.85–1.03), MI (OR 0.79, 95% CI 0.66–0.95), and ischaemic stroke (OR 0.73, 95% CI 0.43–1.22). For those with diabetes: MI (RR 0.86, 95% CI 0.67–1.11), ischaemic stroke (RR 0.62, 95% CI 0.31–1.24).

BLOOD PRESSURE-LOWERING THERAPY:

Treatment should begin with any one of the following agents:

- ACE inhibitor
- Angiotensin receptor blocker
- Calcium channel blocker
- Low-dose thiazide or thiazide-like diuretic.
- If monotherapy does not sufficiently reduce blood pressure add a second agent from a different pharmacological class.

If blood pressure is not responding to pharmacotherapy, reassess for:

• Non-adherence

• Undiagnosed secondary causes of raised blood pressure

• Hypertensive effects of other drugs

• Treatment resistance due to sleep apnoea

• Undisclosed use of alcohol or recreational drugs

• Unrecognized high salt intake (particularly in patients taking ace inhibitors or angiotensin receptor blockers)

• 'white coat' raised blood pressure

• Technical factors affecting measurement

• Volume overload, especially with CKD

The following combinations should generally be avoided:

• Potassium-sparing diuretic plus either ACE inhibitor or angiotensin receptor blocker

• Beta-blocker plus verapamil[Error! Reference source not found.]

LIPID-LOWERING THERAPY:

- Statins should be used as first-line therapy
- If LDL-C levels are not sufficiently reduced on maximally tolerated doses of statin, one or more of the following may be added:
    - Ezetimibe
    - Bile acid binding resin
    - Nicotinic acid.
- Where statins cannot be tolerated at all, one or more of the following can be used:
    - Ezetimibe
    - Bile acid binding resin
    - Nicotinic acid.

- If triglyceride levels remain elevated, treatment with one of the following may be considered:
    - Fenofibrate (especially if HDL is below target)
    - Nicotinic acid
    - Fish oil[21].

CVD RISK ASSESSMENT SCORING SYSTEMS

Scoring systems depend upon assigning a number of points to selected major risk factors. The type and level of risk factor will define the number of points.

It provides a truer picture of risk and can provide numerical cut points for thresholds of interventions.

There are several different scoring systems, a few important scoring systems are:

- Framingham
- PROCAM
- SCORE
- INDIANA

Framingham Scoring System

It is the most popular scoring system; it is based upon data collected during long term follow up of Framingham participants. It has excellent methodology. Points are given to each of the following risk factors:

- Sex
- Age
- Systolic Blood Pressure
- Treatment for Hypertension
- Smoking
- Diabetes
- HDL
- Total Cholesterol

The number of points depends upon the level of the risk factor.

There are different sets of scores for men and women.

Points are added and the total points score can predict the probability of coronary events (nonfatal MI, sudden cardiac death) in next 10 years according to charts.

Global risk assessment is the estimation of the absolute risk based upon the summation of risks contributed by each risk factor.

Coloured risk charts are available and are developed by a number of international societies based upon the Framingham risk equations.

The risk of developing cardiovascular event in 10 years can be defined as:

- Very high when over 40%
- High: 20-40%
- Moderate: 10-20%
- Mild: 5-10%
- Low: less than 5%

Limitations of Framingham Risk Scoring System:

1. It does not account for other established major risk factors, e.g. hypertriglyceridemia, obesity, family history, physical inactivity
2. It does not account for severe abnormalities of risk factors, e.g. severe hypertension, familial hypercholesterolemia, very low HDL-C, heavy cigarette smoking.
3. It underestimates the absolute risk of type 2 diabetes
4. It is limited to white Caucasian population. It may not apply to other populations since risk functions derived from one population may not be valid for risk prediction in other population. It overestimates coronary risk in southern European countries (France, Spain, Italy) and in Japanese, while underestimates risk in South Asian populations. South Asians have higher absolute risk than whites.
5. It does not take into consideration the presence of emerging novel risk factors[23].

PROCAM Scoring System

Based on information collected during 10 years' follow up of 5389 men (35 to 65 years of age) in Germany (Munster).

Endpoints were major coronary events defined as sudden cardiac death or a definite fatal or nonfatal myocardial infarction.

Of the 57 clinical and laboratory variables measured, 8 were found to be independently predictive of event risk. Ranked in order of importance:

- Age
- LDL-C
- Smoking

- HDL-C
- SBP
- Family history of premature MI
- Diabetes
- Triglycerides

The scoring system accurately predicted the coronary events [24].

SCORE Project

This scoring system was developed in 2003

It has the largest data sets from 12 European cohort studies in general population of 205,175 persons including men and women.

End point was 10-year risk of fatal cardiovascular disease

Separate estimate equations were calculated for CHD and for non-CHD and for high risk and low risk regions of Europe.

Two estimated models were developed based upon:

- Total cholesterol
- TC/HDL-C ratio

It is restricted to fatal events only.

High risk is defined in 10-year risk of fatal cardiovascular disease is more than 5%

Risk factors include:

- Age
- Gender
- SBP
- Smoking
- Total cholesterol
- TC/HDL-C [25]

INDIANA Project

The score predicts risk of death from cardiovascular disease in adults with raised BP, based on individual patient data from randomized collected trials.

47088 men and women with differing age ranges followed for a mean of 5.2 years.

A risk score was developed from 11 factors:

- Age
- Sex

- SBP
- Serum total cholesterol
- Serum creatinine
- Cigarette smoking
- Diabetes
- Left ventricular hypertrophy
- History of stroke
- History of MI

Endpoint was 5 years' risk of death from cardiovascular disease, fatal CHD, fatal stroke and all-cause mortality.

INDIANA Project Important Results

- Age is a particularly strong risk factor
- Male sex carries an increased risk. Sex difference narrows with age.
- Median age specific score for men is similar to the median score for women 10 years older.
- Smoking contributed more in women and in younger age groups.
- Total cholesterol is more important in men than in women.
- Total cholesterol and SBP have similar predictive strength in men.
- Diabetes has more predictive effect in women than in men[26].

CONCLUSION

Risk assessment of cardiovascular diseases may show the projected probability of acquiring cardiovascular diseases in the next 10 years based on the patients clinical condition and economic status. The percentage of risk score may vary slightly depending upon the scale used. Calculating the risk may help the patient to change his/her life style or take corresponding precautionary measures to improve his/her health condition.

REFFERENCES

1. "NHS Choices: Your Health, Your Choices". Choice Reviews Online 48.09 (2011): 48-5120-48-5120.
2. Jeemon, P. et al. "Distribution Of 10-Year And Lifetime Predicted Risk For Cardiovascular Disease In The Indian Sentinel Surveillance Study Population (Cross-Sectional Survey Results)". BMJ Open 1.1 (2011): e000068-e000068.
3. http://www.who.int/mediacentre/factsheets/fs317/en/

4. M.Mohsen Ibrahim, Prof. of cardiology- cairo university. A text book of assessment of cardiovascular risk, Cairo; 2005; 38-6.
5. "Guidelines For The Management Of Absolute Cardiovascular Disease Risk".Melbourne; National Heart Foundation of Australia, 2012; 124-20.
6. Brunner EJ, Rees K, Ward K, Burke M, Thorogood M. Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev. 2007(4):CD002128
7. Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J Hypertens. 2006 Feb;24(2):215-33.
8. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. Neurology. 2005 Oct 25;65(8):1193-7.
9. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a metaanalysis of cohort studies. J Nutr. 2006 Oct;136(10):2588-93.
10. Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. Br J Sports Med. 2008 Apr;42(4):238-43.
11. Lollgen H, Bockenhoff A, Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. Int J Sports Med. 2009 Mar;30(3):213-24.
12. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008 Jun;15(3):239-46.
13. Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque IFM, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008(3):CD003054.
14. "Guidelines For The Management Of Absolute Cardiovascular Disease Risk".Melbourne; National Heart Foundation of Australia, 2012; 124-39.
15. Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomized trials. BMJ. 2008 May 17;336(7653):1121-3.
16. Wang JG, Staessen JA, Franklin SS, Fagard R, Gueyffier F.Systolic and diastolic blood pressure-lowering as determinants of cardiovascular outcome. Hypertension. 2005 May;45(5):907-13.
17. Allemann S, Diem P, Egger M, Christ ER, Stettler C. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. Curr Med Res Opin. 2006 Mar;22(3):617-23.

18. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. 2009 May;8(5):453-63.
19. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA. 2006 Jan 18;295(3):306-13.
20. Calvin AD, Aggarwal NR, Murad MH, Shi Q, Elamin MB, Geske JB, et al. Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. Diabetes Care. 2009 Dec;32(12):2300-6.
21. "Guidelines For The Management Of Absolute Cardiovascular Disease Risk".Melbourne; National Heart Foundation of Australia, 2012; 124-56.
22. "Guidelines For The Management Of Absolute Cardiovascular Disease Risk".Melbourne; National Heart Foundation of Australia, 2012; 124-59.
23. Durrington PN, Prais H. Methods for the predication of coronary heart disease risk. Heart 2001;85:489-90.
24. Assmann G, Cullen P, Schulte H. Simple Scoring Scheme for Calculating the Risk of Acute Coronary Events Based on the 10- Year Follow-Up of the Prospective Cardiovascular Munster (PROCAM) Study. Circulation 2002;105:310-315.
25. Conroy RM, Pyorala K, FitzgeraldAP, Sans S, MenottiA, DeBacker G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, on behalf of the SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European Heart Journal 2003;24:987-1003.
26. Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Beissel J-P on behalf of the INDIANA project steering committee. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. BMJ 2001 ;323:75-81.