

# Review of using statins in prevention and management of adverse cardiovascular events.

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**Abstract— Background:** Cardiovascular diseases are a group of heart and blood vessels problems. More than 18 million persons who have cardiovascular diseases die every year.

**Objectives:** To demonstrate the risk factors for adverse cardiovascular events and to describe the uses of statins in prevention and control of adverse cardiovascular conditions.

**Review of literature:** Cardiovascular disease is a major medical problem in all around the world. According to the World Health Organization, in 2011, cardiovascular diseases accounted for about 17.3 million deaths worldwide, and by 2030 this number will grow to more than 23.6 million. There are some risk factors for developing cardiovascular diseases such as: smoking, hypercholesterolemia, overweight, kidney disease, diabetes mellitus and hypertension. Maintaining a healthy diet and healthy lifestyle can help to decrease the risk of developing cardiovascular diseases. Also, baby Aspirin can reduce mortality caused by cardiovascular risk factors if it was taken for more than 10 years. On the other hand, Most of patients who received statins showed a risk reduction of developing cardiovascular diseases. A meta-analysis in 2010 included 76 RCTs reported that statin therapy can decrease all-cause mortality. Cardiovascular diseases mortality was about 27%, non-fatal myocardial infarction 45%, revascularization 95%, fatal myocardial infarction 21%, and fatal and non-fatal strokes about 41%. Statin treatment decreased major cardiovascular diseases and all-cause mortality. Similar studies also proved that statins made a nonsignificant 22.6% relative risk decrease in coronary heart disease mortality.

**Conclusion:** Statins have a good effect on controlling the lipid profile in the body witch is one of the major risk factors of cardiovascular diseases. It was reported that statin therapy decreased all-cause mortality, Cardiovascular diseases mortality was about 27%, non-fatal myocardial infraction 45%, revascularization 95%, fatal myocardial infarction 21%, and fatal and non-fatal strokes about 41%. Although, some studies didn't find a significant reduction effect of statins on the cardiovascular diseases mortality. More studies are needed to approve the effect of statins on the cardiovascular diseases mortality.

**Index terms:** cardiovascular diseases, statins, primary prevention, secondary prevention, cardiovascular diseases prevention.

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## INTRODUCTION

Cardiovascular diseases (CVDs) can be defined as a group of blood vessels and heart problems such as; coronary heart diseases, strokes, peripheral arterial diseases and aortic diseases. They are the first cause of death worldwide (1). Approximately more than 18 million people who have cardiovascular diseases die every year (2). In the six Gulf Cooperation Council (GCC) countries, cardiovascular diseases was found to contribute for 45% of deaths. The highest proportion of deaths caused by the cardiovascular diseases were in Oman and Kuwait (49% and 46%, respectively); Saudi Arabia, United Arab Emirates, Bahrain, and Qatar (42%, 38%, 32%, and 23%, respectively) also had a significant proportion of cardiovascular deaths (WHO country profiles) (3). In Saudi Arabia, related to statistics, cardiovascular diseases increase the amount of deaths every year (4).

There are many ways for treatment and prevention of cardiovascular diseases. One of the most effective ways is changing the lifestyle. In clinical trials, intense lifestyle modifications can reduce the risk factors of cardiovascular diseases such as high blood cholesterol, high blood pressure and triglyceride levels, diabetes, obesity, decrease the physical activity and unhealthy diet (5,6). Moreover, a long-term observational epidemiology studies, suggested that a healthy lifestyle, including discreet diet, no smoking, ideal weight and physical activity, in the middle age years of the life could prevent the progress of cardiovascular diseases risk factors and the cardiovascular events (7,8)

In 2002, the United States Prevention Services Task Force (USPSTF) said that the physicians should discuss the use of baby Aspirin with people who are at high risk of cardiovascular diseases especially coronary heart diseases. The last USPSTF recommendation for using Aspirin as a prevention of cardiovascular diseases was based on collected data from 5 randomized controlled trials (RCTs) which represented a 28% decrease of the risk for myocardial infarction with the use of the baby Aspirin (9).

Statins, also known as HMG-CoA reductase inhibitors, are a [lipid-lowering treatment](#) . Statin is used to decrease the serum [cholesterol](#) as a treatment to decrease the risk of the [cardiovascular disease](#) (10) .

Many studies found that statins can [decrease](#) the [cardiovascular disease mortality and morbidity](#) for people who are at a high risk (11). However, the statins effectiveness in patients without a specific or symptomatic cardiovascular diseases as a primary prevention is not totally clear (12). In 2013 a Cochrane review found that there is a decrease in the risk of death without any evidence of harm if the patient uses statins as a primary prevention of cardiovascular diseases (13).

The current National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines advised to start the use of statin therapy as a primary prevention depending on the patient's cardiovascular disease risk and low-density lipoprotein (LDL) cholesterol level (14). Also , the guidelines by the [American College of Cardiology](#) and the [American Heart Association](#) advised to start the use of statin treatment as a primary prevention of cardiovascular disease in people who have LDL cholesterol  $\geq 190$  mg/dL or those who have diabetes mellitus, at the age of 40 to 75 with LDL cholesterol about 70–190 mg/dl; or with people who are suffering a 10-years risk of progression of stroke of heart attacks of more than 7.5% (15).

The aim of this review of literature is to demonstrate recent knowledge of risk factors of cardiovascular diseases and to assess the primary and secondary preventive measures particularly the effectiveness of statin use in prevention and treatment of cardiovascular diseases.

## REVIEW OF LITERATURE

Cardiovascular disease (CVD) is "a class of diseases that involve the [heart](#) or [blood vessels](#). Cardiovascular disease includes [coronary artery diseases](#) (CAD) such as [angina](#) and [myocardial infarction](#) (commonly known as a heart attack)" (16).

The most common cardiovascular disease is the rheumatic heart disease which is a huge problem in growing countries it leads to approximately 250,000 deaths per year worldwide (17). Another disease is Hypertension (HBP), which is a circumstance of elevation of the blood pressure in the arteries (18). In Saudi Arabia there are more than 24.2% person who have high blood pressure (19). And the most common type is Coronary artery disease (CAD), also recognized as ischemic heart disease (IHD), which is a group of diseases that includes: unstable angina, stable angina, sudden cardiac death and myocardial infarction (20).

### 1. Prevalence of cardiovascular disease and magnitude of the problem:

According to the World Health Organization (WHO); in 2011, cardiovascular diseases accounted for about 17.3 million deaths worldwide through this year, and by 2030 this number is predicted to grow to greater than 23.6 million. More than 75% of cardiovascular diseases deaths happen in low-income and middle-income countries. 80% of cardiovascular diseases deaths are due to stroke and heart attacks (16).

Cardiovascular disease has been the leading cause of mortality in the United States of America since 1900, with the

exception of 1918, the year of the massive influenza epidemic. According to the most recent statistics, if all forms of the most important cardiovascular disease are eliminated, life expectancy would rise almost 7 years. Furthermore, even though cardiovascular disease are often perceived as diseases of older age yet approximately 50% of cardiovascular disease diagnoses and 15% of cardiovascular disease deaths are in patients aged less than 65 years (21).

The majority of killer illnesses in the Kingdom of Saudi Arabia (KSA) are non-communicable, chronic diseases. The WHO, 2008 reported that of the 413 deaths per 100,000 people in KSA in 2002, a 144 deaths (35 percent) were due to cardiovascular event (19). Cardiovascular disease-associated mortalities are the highest worldwide. In Saudi Arabia, cardiovascular disease accounts for more than 22% of deaths every year, and other estimates showed more than 42% of total deaths are attributed to cardiovascular disease in Saudi Arabia (22).

Coronary heart events in KSA represent one of the major health problems as the third most common cause of hospital-based mortality after car accidents and senility (19).

The figures (1,2) are going to explain the distribution of the burden of cardiovascular diseases among males (figure 1) and females (figure 2) worldwide. Saudi Arabia is one of the most affected places around the world with cardiovascular diseases and it is more frequent in males than the females (16).

### 2. Risk factors of cardiovascular diseases:

Obesity is an important risk factor of cardiovascular disease. The incidence regarding weight problems ranged

from about 14% in young people less than 6 years of age to about 83% among adults (19).

A cohort prospective study including participants aged from 25 to 50 years old who were followed from the year 2006 to 2013, found that in 110,502 (72.6%) participants, at minimum of one cardiovascular risk factor (current smoking, hypercholesterolemia, overweight, kidney disease, diabetes mellitus or hypertension) was present. Other important risk factors for cardiovascular diseases include age and sex. For people in their middle age, cardiovascular diseases can be 2 to 5 times more common in men than women, and this risk could vary between populations. On the other hand, in women and men the risk of cardiovascular diseases can be increased with age (23).

Another risk factor is cigarette smoking. It was found that smokers have two times more risk of mortality than non-smokers. In the USA, smoking is considered the reason of 33 % of all deaths from cardiovascular diseases (24).

High blood cholesterol is one of the most important risk factors of the cardiovascular diseases, a prospective studies collaboration meta-analysis, concluded that lowering the total cholesterol plasma concentration of 1 mmol/L can lower the risk of mortality caused by cardiovascular diseases (hazard ratio: 0.83, 95% CI: 0.81–0.85) in individuals (women or men) (25).

Diabetes can be a risk factor of developing cardiovascular diseases, a cohort study done in 2015 involving 1 921 260 person , 34 198 (1.8%) had type 2 diabetes and 1 887 062 (98.2%) did not have diabetes, found that diabetes Type 2 was strongly positive associated with ischemic stroke (OR 1.72, 95%CI 1.52–1.95), stable angina (OR 1.62, 95% CI 1.49–1.77)), peripheral arterial disease (HR 2.98, 95% CI 2.76–3.22), heart failure (OR 1.56, 95%CI 1.45–1.69), and non-fatal myocardial infarction (OR 1.54, 95%CI 1.42–1.67) (26).

### 3. Statins:

Statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors). Statins have been first used in humans in 1980. After that date, a wide variety of treatments from statins have developed (27). The mechanism of action of statins is that they inhibit 3-hydroxy-3-methylglutaryl-CoA reductase in hepatocytes (HMGCR). Statins compete with the HMG-CoA (in a reversible way) for the active site in the reductase. Binding of the statins in the energetic site over the enzyme confers a conformational change that modifies the enzyme's function. Acting as much aggressive antagonists, the greater affinity statins bind to the energetic site of the enzyme, thereby prevent binding of the lower affinity endogenous substrate, HMG-CoA. The result will be the inhibition of HMGCR and thus will decrease cholesterol formation and decrease the intracellular cholesterol which are stored in the hepatocytes (28).

Statins are used to treat hypercholesterolemia and the diseases which can be caused by high cholesterol levels in the body such as the atherosclerotic cardiovascular diseases (ASCVD) (29).

In a cohort prospective study involving 2146 patients who have familial hypercholesterolemia without coronary heart disease and who were followed for 8.5 years; 413 (21%) of the patients started statin as a treatment, and within the follow-up another 1294 patients (66%) were also involved. Most of patients who received statins namely atorvastatin or simvastatin, showed a risk reduction of developing cardiovascular diseases by 76% (hazard ratio 0.24; 95% CI 0.18 to 0.30),  $P < 0.001$  (30).

### 4. Prevention of cardiovascular diseases:

Primary prevention is the first line of care, it's a plan to prevent the occurrence on the disease (31). Lifestyle

modifications such as healthy diet and active aerobic exercise have been found to decrease blood pressure and lipids levels in the body (32). In a cross-sectional study was done to report the relation between the dietary of fiber intake and cardiovascular diseases risk factors in adult women and men, found that the more the dietary fiber intake was associated with lowering the risk of obesity and improve waist-to-hip ratio, decrease the blood pressure, plasma apolipoprotein, triacylglycerol, cholesterol and homocysteine (33).

Many of the risk factors of cardiovascular diseases are modifiable. Information from the Nurses' Health Study, suggest that women who take care of their body weight, eat a healthy diet, do exercise regularly, not smokers can decrease their risk of cardiovascular diseases by 84% (21).

In a study was done in 2013 that included individuals at high risk of cardiovascular diseases, found that a healthy diet associated with nuts or olive oil can reduce the occurrence of major cardiovascular events (34). Also, Baby Aspirin reduces mortality caused by cardiovascular risk factors if it was taken for more than 10 years (35).

Secondary prevention is a plan of care that aims to prevent the recurrence of cardiovascular events or to prevent the complications of cardiovascular disease in people who are already diagnosed with cardiovascular disease (35).

An example for the evidence-based secondary prevention ways for cardiovascular diseases is the multidisciplinary Congestive heart failure management services and the cardiac rehabilitation services (21). In a systematic review that analyzed 47 RCT's studies involving 10,794 patients to cardiac rehabilitation. They found that medium to long term exercise-based cardiac rehabilitation can decrease the cardiovascular mortality [RR 0.74 (95% CI 0.63, 0.87)] and decreases the hospital admissions [RR 0.69 (95% CI 0.51, 0.93)] (36).

There is evidence on the effectiveness of aspirin use as a secondary prevention applied to patients who have stable angina pectoris with no evidence of prior myocardial infraction (MI). A systematic review of antiplatelet treatment for the prevention of vascular diseases found that antiplatelet therapy had similar effects on vascular diseases for patient with a history of myocardial infraction (MI) (12 trials) and with patients who had a history of stable angina (seven trials) (35).

#### **4.1 The role of statins in prevention of cardiovascular diseases:**

For more than 15 years, randomized trials of 3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors (statins), have strongly approved the impact of statins on cardiovascular overall mortality and morbidity in patients with stable coronary artery disease (16).

In a meta-analysis talking about the primary prevention for patients at risk of cardiovascular diseases from moderate to high who had average LDL-Cholesterol levels; using statins as a treatment over about 4.3 years can significantly decrease the relative risk (RR) of major coronary diseases by 29.2%, major cerebrovascular diseases by 14.4%, non-fatal myocardial infarction (NFMI) by 31.7% and revascularization by 33.8% (37).

Another meta-analysis in 2010, included a 76 RCTs all are have the same inclusion criteria including 170 255 patients. Women represented 26% of the participants and the age ranged from 38 to 75 years. Trials followed the participants for 2.7 years on average. There were about 14 878 deaths. It was reported that statin therapy reduced all-causes of cardiovascular mortality. Cardiovascular diseases (CVD) mortality was about 27%, non-fatal MI 45%, revascularization 95%, fatal myocardial infarction (MI) 21%, and fatal and non-

fatal strokes about 41%. The analysis found that statin treatment decreases major cardiovascular diseases and all-cause mortality (38).

A study was done in 2006 including 7 trials with 42 848 patients were involved, 90% had no history of cardiovascular diseases and 10% had a history of cardiovascular diseases. Followed up for 4.3 years in average. Statin treatment decreased the relative risk of major cerebrovascular events, major coronary events, and revascularizations by 29.2%. Also statins created a nonsignificant 22.6% relative risk decrease in coronary heart disease mortality (95% CI, 0.56-1.08) (P=0.13) (37).

In a Cochrane systematic review about statins role as a primary prevention of cardiovascular disease involved eighteen trials with 56 934 individuals, most of them have 1 or more cardiovascular disease risk factors indicated that statins can reduce the risk of developing a cardiovascular disease by about 27% (39).

In a meta-analysis study with involved 70 388 patients with some cardiovascular risk factors, but without any established cardiovascular disease who were randomly arranged to take the statin treatment or the control. It found that statin treatment was associated with a significant risk reduction in all-cause mortality by 12%, major coronary events by 30%, and major cerebrovascular events by 19%. There was a directly proportional reduction about 12% in all-cause mortality per mmol/L decrease in LDL cholesterol (Relative Risk [RR] 0.88, 95% CI 0.84-0.91;  $p < 0.0001$ ) (40). In a Meta-analysis of randomized trials of statins, including 165 792 person, showed that each 1 mmol/L (39 mg/dL) decrease in low-density lipoprotein cholesterol leads to a decrease in the relative risk for stroke of 21.1% (95% CI 6.3–33.5,  $p = 0.009$ ) (41). For primary prevention of cardiovascular diseases, the new ACC/AHA guidelines advice that statin therapy should be

started in individuals with a 10-year ASCVD risk of  $\geq 7.5\%$  (15).

A meta-analysis study of different lipid-lowering therapies, included more than 275 000 individual, found that the statins only (RR 0.87, 95% CI 0.81 to 0.94) and n-3 fatty acids (RR 0.77, 95% CI 0.63 to 0.94) can reduce the total mortality (42). Cardiovascular mortality can be reduced by using statins (RR 0.78, 95% CI 0.72 to 0.84), n-3 fatty acids (RR 0.68, 95% CI 0.52 to 0.9) and resins (RR 0.70, 95% CI 0.5 to 0.99). Also, resins and statins had a significant effect on the lipid-lowering process, n-3 fatty acids wasn't significantly affect the cholesterol level (42).

## CONCLUSION

Cardiovascular diseases are a worldwide major problem as it can affect people from any age, sex and race. It can differ from person to another regarding the presence of the risk factors and its severity. Statins have a good effect on controlling the lipid profile in the body which is one of the major risk factors of cardiovascular diseases. It was reported that statin therapy decreased all-cause mortality, Cardiovascular diseases mortality was about 27%, non-fatal myocardial infarction 45%, revascularization 95%, fatal myocardial infarction 21%, and fatal and non-fatal strokes about 41%. Although, some studies didn't find a significant reduction effect of statins on the cardiovascular diseases mortality. More studies are needed to approve the effect of statins on the cardiovascular diseases mortality.

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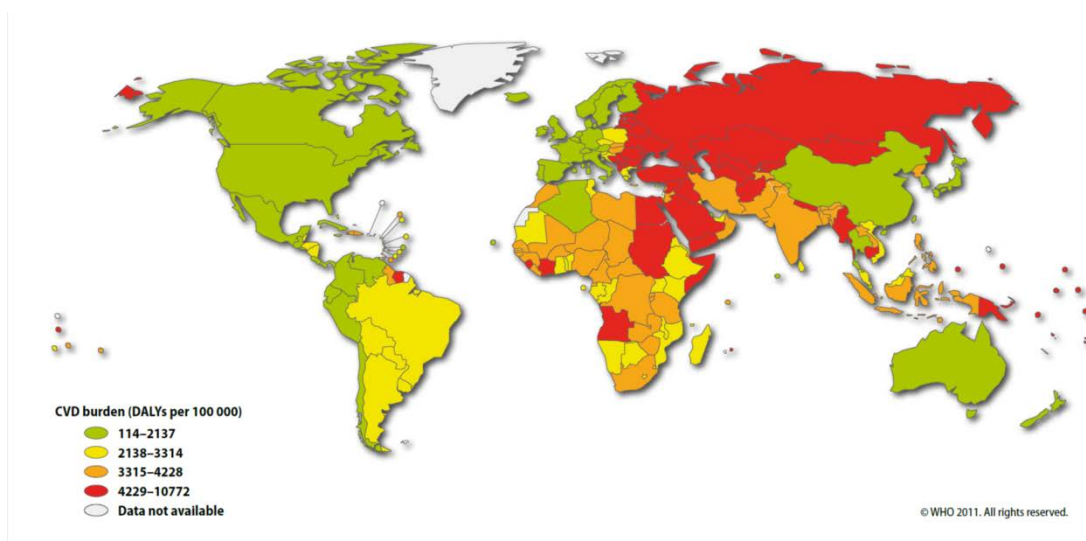
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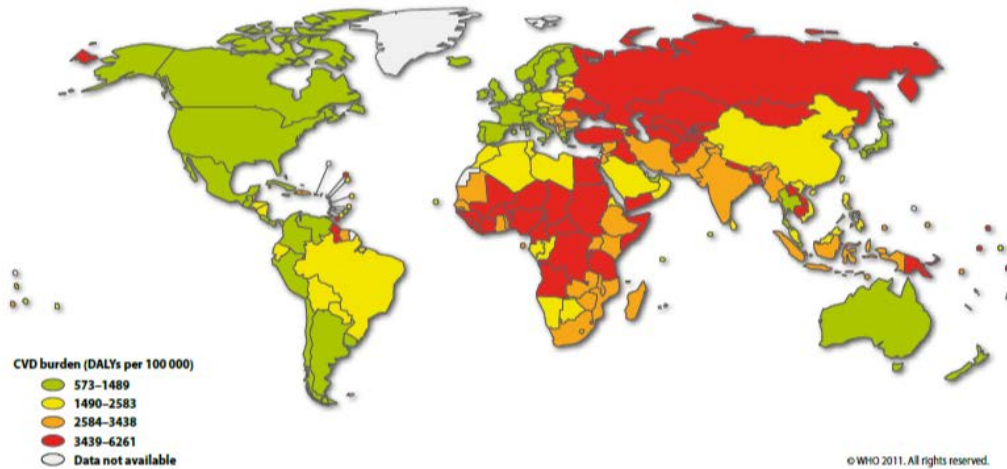
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## FIGURES:



**Figure 1 :** World map showing the global distribution of the burden of CVDs (DALYs), in males (age standardized, per 100 000). From: World Health Organization (WHO), Global Atlas on cardiovascular disease prevention and control 2011, [http://whqlibdoc.who.int/publications/2011/9789241564373\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf).

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**Figure 2 :** World map showing the global distribution of the burden of CVDs (DALYs) , in females (age standardized, per 100 000).

From: World Health Organization (WHO), Global Atlas on cardiovascular disease prevention and control 2011, [http://whqlibdoc.who.int/publications/2011/9789241564373\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf)

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