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Effect of lipid-lowering therapy on the mortality among patients with coronary heart diseases: A systematic review

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Abstract:

Introduction: Studies supported the use of lipid lowering therapy such as statin as a treatment of hypercholesterolemia for prevention of CHD**.** However, the use of lipid lowering therapy is not well established in clinical practice due to lack of robust evidence and contra-indications in patients with heart failure (HF)**.** This review aimed at evaluating the evidence about preventive effect of lipid lowering therapy on the mortality caused by coronary heart diseases. **Methods**: A comprehensive electronic search was carried out using MEDLINE, EMBASE, Cochrane databases to identify articles which aimed at assessing the preventive effect of lipid lowering therapy for coronary heart diseases. The data were collected from included studies using data collection sheets using specific items such as mean patient age, type of coronary disease, mean duration of the disease, drugs of lipid lowering therapy, regime of lipid lowering therapy, duration of lipid lowering therapy, reduction in mortality rate, and associated side effects. **Results**: Following evaluation of the eligible articles, 11 articles were included with randomized controlled trials investigating the effect of lipid-lowering therapy on the mortality of patient suffering from coronary heart diseases. The sample size in the included studies ranged from 106 to 10355 participants, and the total number of participants among all included studies were 50830 with mean age ranging from 31 to 82 years old. **Conclusions**: Despite the overall good outcome that is attributed to the use of statins that is not clear weather this benefit is credited to its anti-inflammatory or direct LDL lowering effect.

Keywords: Lipid, Therapy, Statin, Heart failure, Myocardial infarction

Introduction:

Coronary heart disease (CHD) has been considered as a major factor that contributes to morbidity and debility, particularly among middle aged men [(1)]. Thus, the cardiologist and public health specialists have directed their efforts toward diagnostic and therapeutic methods with continuous updating of the guidelines [(2)]**.** Recently, the preventive interventions have been found to be more cost-effective than curative approach in reduction of morbidity and mortality associated with CHD [(3)].

The corner stone of preventive approach is targeting modifiable risk factors of CHD such as hyperlipidemia, hypertension and smoking [(4)]**.** Guidelines for management of hypertension and hyperlipidemia were postulated to provide basis for CHD prevention [(5)]**.** Hyperlipidemia is a significant risk factor that is characterized by elevated low-density lipoprotein or triglyceride and occasionally low level of high-density lipoprotein [(6)]**.** Studies supported the use of lipid lowering therapy such as statin as a treatment of hypercholesterolemia for prevention for CHD [(7)]**.** However, the use of lipid lowering therapy is not well established in clinical practice due to lack of robust evidence and contra-indications in patients with heart failure (HF) [(7, 8)]**.**

This review aimed at evaluating the evidence about preventive effect of lipid lowering therapy on the mortality caused by coronary heart diseases.

Methods:

A comprehensive electronic search was conducted in MEDLINE, EMBASE, Cochrane databases to identify articles which aimed to assess the preventive effect of lipid lowering therapy in CHD. Search terms included ("coronary artery diseases" OR "heart disease" OR "ischemic heart disease") AND (“lipid-lowering therapy" OR "cholesterol-lowering therapy" OR ezetimibe OR statin OR pitavastatin OR pravastatin OR anacetrapib) AND (mortality OR death). The titles and abstracts of the resultant articles were read by two independent reviewers to identify relevant articles as a primary screening step and to exclude irrelevant, duplicated or review articles. The full texts of these relevant articles were retrieved and the in-depth reading was conducted to exclude the irrelevant articles as a secondary screening step. The articles were assessed against inclusion criteria such as

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clinical trials, published in the last 10 years and written in English language. The population studied should be patients with CHD, while included intervention was lipid lowering therapy. The outcomes assessed were the mortality indicators in rates or percentages. The data were collected from included studies using data collection sheets regarding item such as mean patient age, type of coronary disease, mean duration of the disease, drugs of lipid lowering therapy, regime of lipid lowering therapy, duration of lipid lowering therapy, reduction in mortality, and associated side effects. The review was registered in a registration of systematic review in university of York.

Results:

The electronic searches resulted in a total of 99 articles, of them 67 articles were excluded at the primary screening phase due to irrelevant aims or duplicated publishing. Furthermore, after retrieving of full texts, 21 articles were excluded because of insufficient information, different targeted populations, inconsistent methods or outcomes, or review studies. Finally, 11 articles were included which were randomized controlled trials dealing with the effect of lipid-lowering therapy on the mortality of coronary heart (CH) problems among patients with CHD (Fig. 1). The sample size in the included studies ranged from 106 to 10355 participants, and the total number of participants among all included studied were 50830 with mean age ranging from 31 to 82 years old (Table 1)**.** Regarding the side effects of the lipid lowering agents that have been mentioned in this review, a study found one case of AST and ALT elevation and one case of myalgia in the Rosuvastatin group, also two cases of AST and ALT elevation and one case of myalgia in Ezetimibe group. Beside myalgia, another study showed gastrointestinal discomfort, allergic reactions, psychoneurological symptoms, erectile dysfunction, and edema as adverse effects of Xuezhikang. Studies mentioned liver enzymes abnormalities and myalgia as Atorvastatin side effects. Allergic reaction, myalgia and neurological symptoms have been the unwanted effects of Alirocumab and did not mention any un desirable effects foe their drugs. Many studies focused on myocardial infarction (MI), unstable angina was the diseases that the participants. Other studies targeted population with hypertension (HTN) either alone or accompanied by another CHD. Also, patients with coronary atherosclerotic heart disease have studies by included studies. A verity of medications has been mentioned throughout the studies, Pravastatin, Xuezhikang, Atorvastatin, Alirocumab. Some included studies compared between Ezetimibe and Rosuvastatin or Atorvastatin versus simvastatin. The duration of theses lipid lowering agents use has been ranged from 1- 8 years (Table 1). The reduction in the mortality rate was calculated by different methods, and the majority of the studies revealed that there was no significant difference between the cases and the control groups. Xuezhikang was found to decrease significantly the risk of CHD death by 29.2% and one included study reported no death. Death from coronary heart disease due to Alirocumab use is less than in placebo user group (4 Alirocumab, 7 placebo). Two studies have used markers to determine the drugs effect.

Figure (1): Flow diagram of the included studies in the systematic review

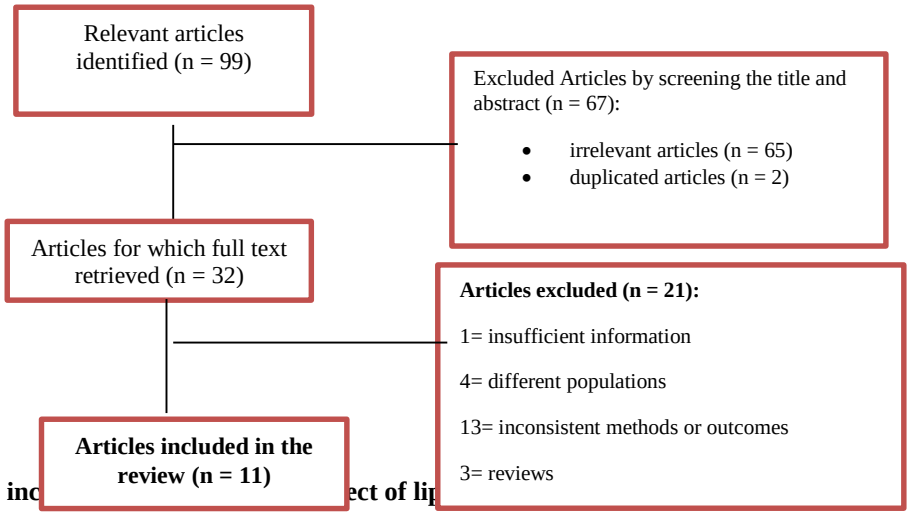

Table (1): The outcomes of the inc ect of lip

Study	Sample size	Patient age	Type of coronary disease	Mean duration of the disease	Drugs of lipid lowering therapy	Regime of lipid lowering therapy	duration of lipid lowering therapy	Reduction in mortality	Side effects
(9)	106 male patients	63±10 in Ezetimibe group 65±12 in Rosuvastatin	Coronary atherosclerotic heart disease	Not reported	Ezetimibe (n=55) Rosuvastatin alone (n=51)	Ezetimibe (10mg, once a night) plus rosuvastatin (10mg, once a night) Rosuvastatin alone (10mg, once a night)	12 months	The cardiac death was 0 in both groups	1 case of AST or ALT > 3 ×ULN 1 case of myalgia 2 cases of AST or ALT > 3 ×ULN 1 case of myalgia
(10)	9014 patients	31 to 75 years (7498 men, 1516 women)	MI / unstable angina	3-36 months previously	Pravastatin	40 mg	1 year	Lp-PLA2 activity levels were reduced by 16%in the pravastatin group	Not reported
(11)	1530	> or = 65-years-old	HTN + Previous MI	Had 28 MI days and 5 years before entering the study	Xuezhikang (n = 772) partial extract of red yeast rice containing statin placebo (n = 758)	0.6 g twice daily	Average of 4.5 years	Xuezhikang significantly decreased the risk of CHD death by 29.2%.	Gastrointestinal discomfort, allergic reactions myalgia, psychoneurological symptoms, erectile Dysfunction, and edema.
(12)	2442 patients	Comparing between 65-78 years old patients and < 65 years old	Myocardial infarction Unstable angina Congestive heart failure	Not reported	Atorvastatin	10 mg/d up to the maximum dose 80 mg/d	53.9 months	Reduction in cardiac death + nonfatal MI in Atorvastatin group	Elevations (>3 times the upper limit of normal) of aspartate aminotransferase levels alanine aminotransferase levels both of them is greater in the older group
(9)	1902	Women mean age (63.5) Men mean age (60.4)	Myocardial infarction (MI previous or present angina	Not reported	Atorvastatin	10 mg/day 80 mg/day (intensive)	4.9 years.	Non-significant reduction in CHD deaths	Myalgia Liver function test up normality
(13)	2867 1467participants on prava And 1400 participants on usual care	65 to 74 years and ≥ 75 years	HTN with at least one CHD	Not reported	Pravastatin sodium Vs Usual care (UC)	40 mg/d	6 years	Non-significant difference CHD death	Not reported
(14)	2341 patients	The mean age 60 years	68.9% of the patients had a history of coronary heart disease (all Patients are already on statin therapy)	Not reported	Alirocumab or placebo	Alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks	for 78 weeks	Death from coronary heart disease, including death from unknown cause 4 patients And 7 in placebo group	General allergic reaction Myalgia Neurologic event
(15)	3,522 1,765 males	Patients aged 70-82	History of or risk factors for CVD	Not reported	Pravastatin Versus Placebo	(40 mg)	3.2 years.	No significant difference in CHD mortality	Not reported

	1757 females								
(16)	7,863 patients	31-75 years	MI or Unstable angina	Not reported	Pravastatin or Placebo	40 mg per day	6 years	Higher baseline TnI levels were associated with a larger absolute benefit of pravastatin and therefore fewer numbers needed to treat.	Not reported
(17)	10,355 participants	≥55 years	HTN	Not reported	Pravastatin (n=5170) or usual care (n=5185)	(40 mg/d)	4 to 8 years	No significant differences between groups	Not reported
(18)	8,888 participants	≥65 years versus <65 years	Myocardial infarction	Not reported	Atorvastatin versus Simvastatin	(80 mg/day) (20 to 40 mg/day)	1 year	No significant difference regarding cardiovascular death	Muscle and liver abnormalities Myopathy Rhabdomyolysis

Discussion:

A review of eleven randomized controlled trials (RCTs) studies, included a wide range of patients from (106-10355) were involved in the present study. This large population size is considered a positive factor and a point of strength in this review [(13)] .The participants were of old age (31-82) aiming at observing the effect of lipid-lowering therapy on the mortality of coronary heart (CH) problems among patients with CHD and other comorbidities. Procedures and guidelines have been directed toward prevention of the consequences of chronic heart disease [(2)], one of these prophylaxis measurements is the lipid lowering agents (statin and others) which were founded to be of great value in decreasing the mortality rate in patients of old age [(1)]. LDL and cholesterol levels should be in their minimum range. Resulting in that most of the lipid lowering agents were not significant in reducing the mortality rate. That may be partially attributed to that most of the control groups were using (usual care) which is consisting of a lipid lowering drug plus major adjustment that were done to improve the daily life style [(19)].

The follow up period needed to be longer for better effects observation, this will also help in detecting new side effects and give a time for informative testing of these adverse effects [(19)]. The studies with significant results containing statins as the drug of choice with fair effect, for that statins holds the record of being the best agents in lowering the LDL levels [(20)]. Furthermore, statins had a side effect profile that is tolerable for most patients but not that much for high risk old patients as studies documented that it's effect with muscle ache and lack of proper muscle function. In addition, few cognitive side effects accompanying their use that is why more attention is needed to be addressed regarding this issue [(21)]. Fortunately, studies demonstrated that using statins with a significantly high dose (aggressive treatment) in old patient affect the result of LDL level thus enhancing the overall health status [(22)] of the patient especially those ailments that are related to the cardiovascular events [(13, 23)].

Conclusions:

This review concluded that, there was no clear results regarding effect of statins, and other lipid lowering medications, in reduction of the mortality rate that is caused by cardiovascular events. Despite the overall good outcome due to the use of statins, it was not clear weather this

benefit is credited to its anti inflammatory or direct LDL lowering effect.

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