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REVIEW ARTICLE

Meta-Analysis of Lowering LDL Cholesterol and its Impact on the Cardiovascular System

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ABSTRACT

Background: By lowering LDL cholesterol levels, the risk of coronary heart disease (CHD) and other serious vascular events can be significantly reduced. In order to prevent cardiovascular illnesses (CVD), mainly coronary heart disease, LDL-cholesterol (LDL-C) levels must be tightly controlled on both a primary and secondary level (CHD). Despite the fact that patients in primary prevention experience a higher absolute number of atherosclerotic cardiovascular (CV) events than those in secondary prevention of CVD, subjects in primary prevention frequently receive little attention when it comes to the clinical management of LDL-C levels.
Aim: To summarise the research supporting LDL cholesterol reduction treatments for elderly people.
Method: For this meta-analysis, we searched PubMed, GOOGLE SCHOLAR, SCI.HUB, MEDLINE, and Embase for publications released between January 1, 2017, and December 28, 2021. As recommended by the 2018 American Academy of Cardiology and American Heart Association guidelines, randomised controlled trials evaluating cardiovascular outcomes of an LDL cholesterol-lowering medicine with a median follow-up of at least 2 years and data on older patients (aged 75 years).The search for literature source was limited to randomized controlled trials (human being). This meta-analysis, comprised of 24 trials from the Cholesterol Therapy Trialists' Collaboration meta-analysis plus five other trials, used data from six journals. 21492 (8%) of the 244090 participants in 29 studies, were over the age of 75. Among them, 11750 (54%) came from statin trials, 6209 (28%) from ezetimibe trials, and 3533 (16%) from PCSK9 inhibitor trials. We conducted network meta-analyses for the statins and non statin treatments.
Results: Of the 244090 participants in 29 studies, 21492(8%) were over 75. These included 3533 (16%) from PCSK9 inhibitor studies, 11750 (54%) from statin trials, and 6209 (28%) from ezetimibe trials. A median follow-up period of 2 to 6 years was used. Without statistically differentiating from the risk reduction in patients under the age of 75 (085 [078-092]; pinteraction=037), LDL cholesterol lowering significantly reduced the risk of major vascular events (n=3519) by 26% for 1 mmol/L reduction in LDL cholesterol (RR 074 [95% CI 061-089]; p=00019).In older patients, there was no statistically significant difference in the RRs for statin (0.82 [0.73-0.91] and non-statin (0.67 [0.47-0.95]; pinteraction=0.64) treatment. Reduced LDL cholesterol in older persons was shown to benefit all components of the composite, including coronary revascularization (080 [066-096], stroke (073 [061-087], and myocardial infarction (080 [071-090].
Practical implication: This meta analysis can be used to improve the treatment of people withlowering LDL cholesterol.
Conclusion: The viability and security of diminishing LDL cholesterol in more seasoned adults are now supported by further research provided by this meta-analysis. By non-statin and statin LDL cholesterol-bringing down medication, we identified a risk reduction for major vascular events that were at least as effective as that observed in younger patients
Keywords: LDL, Meta-analysis, Cardiovascular, Cholesterol,Atherosclerosis, Primary and secondary prevention.

INTRODUCTION

LDL cholesterol has long been recognized as a given risk for cardiovascular disease caused by atherosclerosis. In a wide spectrum of individuals, encompassing women and men, individuals at minimal risk of cardiovascular events, elderly persons, statin medication can reduce the risk of serious vascular events, and people with high cholesterol, according to researchers from the CTT (Cholesterol Treatment Trialists') alliance. However, as evidenced by variations in the recommendations among the leading cardiology societies, there is still debate regarding the best strategy for decreasing LDL cholesterol, especially in light of new LDL cholesterol-reduction therapies Ezetimibe with inhibitors of PCSK9 (proprotein convertase subtilisin/Kexin type 9)[1].

It's uncertain if targets of cholesterol or reduction in percentage should be established as therapy objectives. Concerning essential anticipation, the accentuation currently is on involving LDL cholesterol shorts and hazard-adding machines for cardiovascular illness to coordinate the beginning of prescription. As per the American School of Cardiology/American Heart Affiliation (ACC/AHA) and Canadian Cardiovascular Society (CCS) rules, high-risk patients ought to have an objective LDL cholesterol centralization of >1.8mmol/L or a decrease in LDL cholesterol of over half from the benchmark. There is debate over the relative benefits of employing LDL cholesterol upper limits alone, deciding how much LDL cholesterol reduction should be pursued, and defining particular therapy goals[2].

Clinical studies of treatments that reduce the level consistently, of LDL cholesterol demonstrated a decrease in the hazard of coronary events. Since members aged 75-78 years or more weathered were underrepresented in several trials, the clinical impact of decreasing LDL cholesterol in elderly adults is still up for dispute. Through the therapy of statin or a more rigorous statin regimen, major cardiovascular events were reduced in the CTTC by 21% per 1 mmol/L decline in LDL, albeit there may have been some retardation in older patients[3]. For elderly patients, the 2018 cholesterol guidelines of ACC/AHA guidelines are less strong than they are for younger people. The 2019 European Culture of Atherosclerosis dyslipidemia Society and Cardiology rules support treating more aged individuals, yet they additionally incorporate explicit suggestions to assess comorbidities preceding the beginning of treatment. Studies have shown that in clinical practice, elderly patients—an important cohort that makes up about 20% of the population8—use cholesterol-lowering less frequently than younger individuals[4].

The risk factor of cardiovascular occasions is high for patients with atherosclerotic cardiovascular sickness or disease (ASCVD), and the gamble of a recurrent occurrence is significantly higher for people who have had a new history of a cardiovascular

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occasion (within the beyond a year). Intense coronary condition (ACS) or a background marked by myocardial ischemia, steady or shaky angina, coronary revascularization, ischemic stroke, transient ischemic assault, or fringe blood vessel sickness is normal judgment for patients with clinical ASCVD. To decrease the gamble of future cardiovascular occasions, low-thickness lipoprotein cholesterol (LDL-C) ought to be diminished. The utilization of maximally endured statins for the lessening of LDL-C in patients with ASCVD was recommended by the 2018 multi-society direction on the administration of blood cholesterol. Notwithstanding, numerous patients with clinical ASCVD will in any case require extra lipid-bringing medicines furthermore down to statin treatment to accomplish LDL-C levels under 70 mg/dL[5].

The genetically determined apolipoprotein (a) and apolipoprotein B-100 moieties of low-density lipoprotein lipoprotein(a) are hypothesised to exhibit pro-atherogenic, pro-thrombotic, pro-inflammatory, and pro-oxidative properties. High levels of lipoprotein(a) have been linked to incident cardiovascular disease in the majority of population-based epidemiological studies and in individuals with existing coronary heart disease, though not always. Also, a Mendelian randomization research demonstrates a linear relationship between the prevalence of lipoprotein (a) in the general population and acute coronary heart disease [6]. According to the existing data, European (but not American) guidelines suggest that lipoprotein(a) is a reasonable target for treatment if concentrations are 50 mg/dl [6,7]. Given how effective 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are at lowering cholesterol, it was simpler to evaluate whether a marked drop in LDL cholesterol concentrations would result.Statins have established themselves as a first-line treatment for decreasing low-density lipoprotein cholesterol due to their effectiveness and ability to reduce the risk of events (LDL-C). Absolute cardiovascular (CV) risk can be decreased by lipid-lowering drugs, depending on the patient's baseline CV risk and the extent of LDL-C reduction. According to randomised controlled studies, statin therapy generally appears to have modest rates of myalgia, myositis, and rhabdomyolysis; nevertheless, observational and patient-report data indicate that the prevalence of statin-related muscle problems in clinical practise may be as high as 29%. An increased risk of CV non-fatal events has been linked to statin intolerance[8,9].

The identification of the main patient populations receiving statin medication underwent a substantial change in the 2013 ACC/AHA blood cholesterol management guidelines, which also placed a heavy emphasis on the use of higher-intensity statin regimens [10]. When LDL- and non-HDL-cholesterol levels remained over set criteria after statin medication, an expert consensus panel from the ACC recommended employing nonstatin therapies (ezetimibe and PCSK9 inhibitors) in addition to maximally tolerated statin therapy. Due to the enormous benefits statin medication offers in the primary and secondary prevention of cardiovascular disease, it has received attention about its long-term safety. Statins have shown significant benefits in the primary and secondary prevention of coronary and cerebrovascular disease events by inhibiting 3-hydroxy-3-methylglutarylCoA reductase most of these investigations were conducted. The need for such medication in patients older than 70 years of age, who typically die from vascular disease, is less clear because the relationship between plasma cholesterol and risk of coronary artery disease weakens with age. Hypertension and stroke frequency are both associated with vascular disease in the elderly, but plasma cholesterol is not[11].

We began the prospective research of pravastatin in the elderly at risk because it was important to balance the effectiveness and safety of lowering cholesterol in older people (PROSPER). Our aim was to investigate if pravastatin reduces the risk of cardiac events, strokes, cognitive deterioration, and disability in people with vascular disease as well as those who are at high risk of getting it (primary prevention). We judged that a treatment period of at least three years was an appropriate time frame to investigate the efficacy of the medicine in what for many people is the last decade[12,13].

Our objective is to conduct a meta-analysis of the pertinent data from important random trials for approved treatments to decrease LDL cholesterol and to study the effects of inhibitors for lowering LDL cholesterol.

METHOD

While performing this systematic review and meta-analysis, the PRISMA guidelines were adhered to. According to the 2018 ACC/AHA guidelines, this review performed an unrestricted search of MEDLINE, GOOGLE SCHOLAR, SCI.HUB, and Embase between March 1, 2015, and August 14, 2020 for all randomised, controlled, cardiovascular outcome trials of the LDL cholesterol-lowering drugs (statin, ezetimibe, evolocumab, and alirocumab). Data from 24 trials from the CTTC meta-analysis were used in this meta-analysis, which we conducted using information from six articles. 21 492(8%) of the 244 090 patients from 29 trials who were randomly allocated were elderly (at least 75 years old).These included 3533(16%) from PCSK9 inhibitor studies, 11750(54%) from statin trials, and 6209(28%) from ezetimibe trials. The majority of trials met the criteria for minimal risk of bias, according to the Cochrane method for assessing bias in randomised clinical trials. Between two and six years was the average length of the follow-up[4]. The inaugural outcome study for these indicated non-statin medications was published in 2015 using a standard for individuals aged at least 75 years, while the CTTC reported results for statins in older patients in 2019. Consensus was reached to resolve any differences.The CTTC meta-analysis included statin therapy data. 5 We combined data from 24 statin trials that included elderly patients (>75 years) and eliminated four trials that only included dialysis or heart failure patients. The basis for this finding was the 2018 US and 2019 European guidelines, which do not recommend lipid-lowering medication in patients with severe renal disease or heart failure without additional indication. The Treat Stroke to Target trial (target LDL cholesterol 18 mmol/L [70mg/dL] vs. 23-28mmol/L [90-110 mg/dL]) and the CTTC meta-analysis were two of the 24 studies from the statin trials (statin or more intensive statin vs. placebo or less intensive statin).The non-statin studies included IMPROVE-IT (ezetimibe 10 mg vs placebo, along with simvastatin), EWTOPIA (ezetimibe 10 mg against standard care), FOURIER (evolocumab vs placebo, along with maximally tolerated statin medication), and ODYSSEY OUTCOMES (alirocumab vs placebo, in addition to maximally tolerated statin therapy). Every elderly patient in the non-statin research, whose mean age was 79 years and whose gender distribution was 4792 (49%) women and 4950 (50%) men, had their demographic information provided[4].

Data selection: Data for statin therapy were provided by the CTTC meta-analysis. We collected aggregated data on older individuals (aged >78 years) from 25 statin trials, leaving out 4 trials that only involved heart patients with failure or those undergoing severe kidney dysfunctioning or on dialysis[1]. The 2018 United States and 2019 standards of European society, which don't suggest therapy for lowering lipids in individuals with advanced kidney problems or heart failure who do not have another justification, served as the foundation for this conclusion[4].

Data collection: Seeing as all of these events have been shown to be decreased by treatments of LDL lowering, conclusions from every preliminary were chosen to most intently look like the target complex endpoint of foremost vascular actions, which included death caused by cardiovascular, infraction by acute myocardial or other syndromes related to acute coronary, revascularization of coronary, or stroke when available. In certain cases, the chosen outcome that most closely matched the goal composite served as the trial's secondary composite endpoint. Additionally, we looked at non-cardiovascular demise and all-cause passing, as well as the singular components of the composite result. To examine the therapeutic effects of older and younger patients, we retrieved data

from participants who were under the age of 78. Since the more youthful information from the Treat Stroke to Target preliminary was separated into 2 age gatherings (66 years and 66-78 years), we utilized a proper impact strategy to measure the impact in more youthful patients. There were available safety outcomes of interest for malignancy, hemorrhagic stroke, newly diagnosed diabetes, and neurocognitive adverse events[14,15,16].

Analysis of Data: To compare the therapy effects of older and younger patients, we retrieved data from participants who were under the age of 75. We used a fixed effect approach to estimate the effect in younger patients because the younger data in the Treat Stroke to Target trial were reported by two age categories (patients under 65 and patients between 65 and 75). There were available safety outcomes of interest for malignancy, hemorrhagic stroke, newly diagnosed diabetes, and neurocognitive adverse events[17].

For each trial, the rate ratio or HR (hazard ratio) and 95% of CI were mined and regularized per 1 mmol/L (40–68 mg/dL) variation in LDL. A risk ratio (RR) was computed in the absence of the HR or rate ratio. The effect estimate was described using RR after the findings were pooled. We estimated 95% CIs before pooling with other trials because the rate ratios in the age groupings in the CTTC were reported with 99% CIs. The variability of preliminaries in lipid-bringing down drugs, follow-up span, and study populaces were taken into account using an irregular impacts meta-examination with a limited greatest probability approach. For the essential and optional endpoints, patients were divided into groups based on whether they were receiving statin[1] or non-statin[16] therapies for lowering cholesterol (LDL). On behalf of the prime endpoint, patients were divided into groups based on whether they had established atherosclerotic cardiovascular disease or not. With the use of Q statistic by Cochran's, Higgins, and Thompsons' I2 statistic, and normal scattering as a result of sizes, we evaluated heterogeneity. By removing concentrates that were in danger of predisposition and utilizing the Hartung-Knapp change, responsiveness examinations for the essential endpoint were directed after the gamble of inclination was resolved involving the Cochrane technique for surveying hazard of predisposition in randomized clinical preliminaries. Utilizing Egger's relapse test and a pipe chart, distribution predisposition for the essential result of major vascular occasions was evaluated[16].

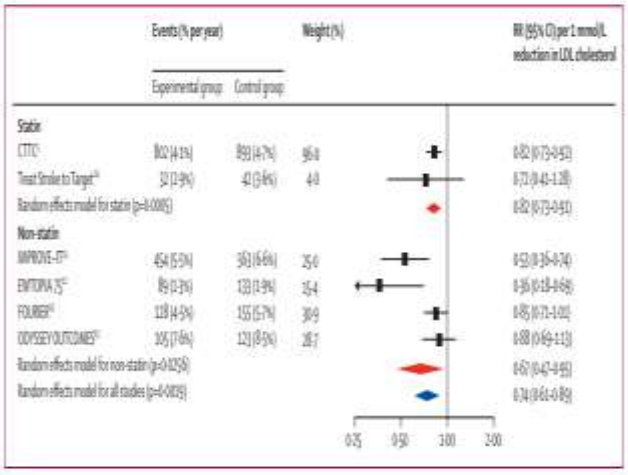
For security endpoints, proportions rate or HRs and CIs with 95% were extrapolated from the first preliminaries, if accessible, or a RR was determined from crude totals for every preliminary. After normalizing 1 mmol/L per RR decline in LDL, the meta-examination was directed utilizing an irregular impacts model with a confined greatest probability approach. R (variant 3.6.1) and the R bundle were used to conduct statistical analyses (version 2.0-0)[16].

RESULTS

With a weighted mean of 2mmol/L (107.6mg/dL) and SD of 0mmol/L (25.9mg/dL), baseline LDL cholesterol levels in the experimental groups ranged from 2 mmol/L (77.8mg/dL) to 4 mmol/L (162.0mg/dL). Following randomization, the experimental group's mean LDL cholesterol readings ranged from 0 mmol/L (40 mg/dL) to 3 mmol/L (123 mg/dL). The mean reduction in LDL cholesterol ranged from 04mmol/L (136 mg/dL) to 13 mmol/L (515 mg/dL), with a weighted mean of 09 mmol/L (362 mg/dL) and SD of 04 mmol/L (149 mg/dL).

At the time of randomization, out of 255690 patients enrolled in 29 studies, 20292 (7.9%) were elderly (at least 75-78 years old). Of these, 10750 (55%) belonged to statin trials, 5919 (29 %) to ezetimibe trials, and 4233(15%) to PCSK9 inhibitor trials. The Cochrane method for determining the bias risk in clinical studies that are random found that the majority of trials satisfied the requirementsfor tolerability of inclination. The median follow-up lasted between two and six years. The statin trials included 25 studies from the Treat Stroke to Target preliminary (target LDL 17.9 mmol/L [72 mg/dL] vs. 25-30 mmol/L [95-115 mg/dL]) and the CTTC meta-examination (statin or more serious statin versus fake treatment or less concentrated statin) [1]. The non-statin preliminaries included IMPROVE-IT, which contrasted ezetimibe 10 mg with a fake treatment notwithstanding simvastatin, EWTOPIA 75, which contrasted ezetimibe 10 mg with standard consideration, FOURIER, which contrasted evolocumab with a fake treatment notwithstanding maximally endured statin treatment, and ODYSSEY Results, which looked at alirocumab. Segment data accommodated all more seasoned patients in the non-statin studies, whose mean age was 80 years old and whose gender composition was 4812(49%) women and 4890(50%) males. The treatment results revealed in preliminaries including more established and more youthful people (matured 78 years) are compiled[16,17].

Figure1: Impact of LDL reduction on the incidence of foremost cardiovascular diseases in older individuals receiving statin therapy and non-statin therapy[16].



In the control groups, the weighted rate of major vascular events was 41% per year for younger patients versus 57% per year for older patients. Every 1 mmol/L reduction in LDL cholesterol, lipid-lowering treatments decreased the incidence of major vascular events in older adults by 26% overall. With no statistically significant interaction (pinteraction=037), the risk reduction's magnitude was statistically comparable to that observed in younger patients.The risk ratios (RRs) per 1 mmol/L decrease in LDL cholesterol in older patients did not differ statistically between statin and non-statin treatment. Similar to this, we discovered no evidence of a treatment difference between patients at baseline with and without established atherosclerotic cardiovascular disease.

Lipid-lowering treatments lowered coronary revascularization, myocardial infarction, and stroke risk in older individuals by 20%, 27%, and 27%, respectively, for every 1 mmol/L reduction in LDL cholesterol. With the exception of stroke, where the risk reduction was marginally larger with non-statin than with statin, the treatment effect magnitudes in older patients were not statistically different for statin and non-statin trials. The expected result was that cholesterol lowering had no impact on non-cardiovascular death. The all-cause mortality rate was 093 (95% CI 084-102; p=013).

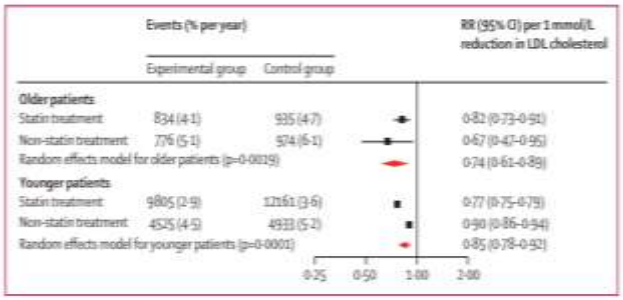
The overall treatment impact for the major vascular events endpoint among older patients was similar when all the trials were combined with the Hartung-Knapp method of adjustment (RR 074 [95% CI 055-098]). We discovered a fair amount of variability between the studies (I2=6761%). The heterogeneity, however, significantly diminished (I2001%) when the smallest open-label trial (EWTOPIA 75) was omitted, and the impact estimate remained to

provide a significant advantage for cholesterol lowering (RR 081 [95% CI 074-088]).

Similar results were obtained for major vascular events in sensitivity analyses that did not include the trials that were at risk of bias (Treat Stroke to Target and EWTOPIA 75). (081 [074-089]). Although though the EWTOPIA 75 study only contributed 66% of the entire pooled result to the sensitivity analysis, it still showed a significant effect for decreasing cholesterol in older patients.

In studies comparing statin and non-statin groups, each 1 mmol/L drop in cholesterol was not linked to a higher risk of cancer in older people[4].

Fig.2: Outcome of reducing LDL cholesterol on serious cardiovascular risk in older individuals as compared to younger people[16].



DISCUSSION

The safety and effectiveness of decreasing LDL cholesterol in elderly individuals are now supported by further research provided by this meta-analysis. Using statin & non-statin LDL cholesterol-lowering medication, we clearly identified a risk reduction for major vascular events that was at least as effective as that observed in younger patients. Additionally, all of the individual endpoints—including cardiac mortality, ischemic stroke, stroke, and coronary revascularization—saw significant decreases [20,21].

Major vascular events are more common in older people. In our meta-analysis, those 78 years of age and older experienced major vascular events at rates that was nearly 42% higher than those under 75 years old. Therefore, the genuine risk decreases expected from serving more aged patients ought to be greater than those in treating more youthful patients given the same relative risk decreases showing up over a couple of long periods of treatment. In high-income nations, men's life expectancy at age 65 is about 20 years, while it is higher for women. This means that there is an average opportunity of at least a decade to prevent cardiovascular disease in patients who are 78 years old[22,23]. Furthermore, coronary heart disease continues to be the number one killer of seniors. We further stress that the information support keeping up with LDL cholesterol appropriately controlled as soon as doable in people to stay away from the beginning of atherosclerosis, in spite of the way that we have shown an unmistakable viability for lipid decrease in more established patients [24,25,26,27]. As a matter of fact, epidemiological examinations uncover somewhat low occurrence of cardiovascular sickness in social orders where the typical LDL cholesterol is beneath or equivalent to 18 mmol/L, and coronary imaging studies show plaque withdrawal when LDL cholesterol is underneath around 18mmol/L. Consequently, the execution of lipid-bringing meds prior in life down to support the anticipation of atherosclerosis ought not be precluded provided our capacity to treat people with atherosclerosis and the illness' concerns in more seasoned patients[28,29,30].

CONCLUSION

In high-income countries, those aged 75-78 and older, make up over 20% of the population. Lower rates of cholesterol-lowering medications are used in this significant population segment than in younger patients because of concerns about smaller relative hazard decreases, more limited span to impact hazard of cardiovascular results, and expanded frequency of side cases. The ACC/AHA cholesterol guidelines offer distinct advice for treating lipid reduction in older individuals as opposed to younger ones. In particular, the strategies indicate a class I high-intensity statin for patients having ASCVD who are not at incredibly excess hazard and a class IIb proposal for the expansion of ezetimibe if the LDL stays 16 mmol/L (69.8 mg/dL) or more prominent. Conversely, there is no idea for the consideration of a non-statin in patients more seasoned than 75 years, and just a class II solution is made for a statin, which can be either moderate or extreme focus. Besides, proposals for the utilization of treatment of statin in high-risk populaces, like those with extreme hypercholesterolemia, diabetes, or as essential avoidance, were undeniably made for patients b/w the ages of 45 and 78, whereas no specific advice was provided for those who were 75 to 78 years old or older. The amount of proof in more seasoned patients was generally seen to be weak.

The viability and security of diminishing LDL cholesterol in more seasoned adults are now supported by further research provided by this meta-analysis. By non-statin and statin LDL cholesterol-bringing down medication, we identified a risk reduction for major vascular events that were at least as effective as that observed in younger patients. Additionally, the entire singular cutoff comprising cardiovascular demise, myocardial dead tissue, stroke, and revascularization of coronary arteries showing significant decreases.

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